A STUDY ON THE CLINICAL PROFILE,BLOOD PROFILE AND BLOOD CULTURE SENSITIVITY PATTERN OF SALMONELLA TYPHI IN PAEDIATRIC PATIENTS OF PSGIMS & R

Dissertation Submitted to

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

In fulfilment of the regulations for the award of the degree

M.D. (PAEDIATRICS)

DR.RIYAS CHUNGATHU

POST GRADUATE STUDENT

DEPARTMENT OF PAEDIATRICS

PSG INSTITUTE OF MEDICAL SCIENCE AND RESEARCH

PEELAMEDU, COIMBATORE -641 004

APRIL 2013

A STUDY ON THE CLINICAL PROFILE, BLOOD PROFILE AND BLOOD CULTURE SENSITIVITY PATTERN OF SALMONELLA TYPHI IN PAEDIATRIC PATIENTS OF PSGIMS & R

Dissertation Submitted to

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

In fulfilment of the regulations for the award of the degree

M.D. (PAEDIATRICS)

DR.RIYAS CHUNGATHU

POST GRADUATE STUDENT

DEPARTMENT OF PAEDIATRICS

PSG INSTITUTE OF MEDICAL SCIENCE AND RESEARCH

PEELAMEDU, COIMBATORE -641 004

GUIDE

DR.A.M.VIJAYALKSHMI DCH, MD

PROFESSOR AND CHIEF UNIT TWO, PAEDIATRICS

APRIL 2013

CERTIFICATE

This is to certify that the thesis entitled "**A STUDY ON THE CLINICAL PROFILE,BLOOD PROFILE AND BLOOD CULTURE SENSITIVITY PATTERN OF SALMONELLA TYPHI IN PAEDIATRIC PATIENTS OF PSGIMS & R"** is the bonafide work of Dr. RIYAS CHUNGATHU done in the department of Paediatrics , PSG Institute of Medical Sciences and Research, Coimbatore under the supervision of Dr.A.M.VIJAYALAKSHMI, Professor and Chief Unit two, Paediatrics in fulfilment of the regulations of the Tamil Nadu Dr.MGR Medical university for the award of MD degree in Paediatrics

DR.RAMALINGAM

PRINCIPAL

PSG IMS&R

DECLARATION

I hereby declare that this dissertation "**A STUDY ON THE CLINICAL PROFILE,BLOOD PROFILE AND BLOOD CULTURE SENSITIVITY PATTERN OF SALMONELLA TYPHI IN PAEDIATRIC PATIENTS OF PSGIMS & R"** is my bonafide work and prepared by me under and supervision of DR.A.M.VIJAYALAKSHMI, Professor and unit two Chief, Paediatrics, PSG Institute of Medical Sciences and Research, Coimbatore. The dissertation is submitted to The Tamil Nadu Dr.MGR Medical University in fulfilment of the University regulation for the award of MD degree in Paediatrics. This dissertation has not been submitted for the award of any other Degree or Diploma in this for any other University.

DR.RIYAS CHUNGATHU

CERTIFICATE BY THE GUIDE

This is to certify that the thesis "**A STUDY ON THE CLINICAL PROFILE, BLOOD PROFILE AND BLOOD CULTURE SENSITIVITY PATTERN OF SALMONELLA TYPHI IN PAEDIATRIC PATIENTS OF PSGIMS & R"**is the bonafide work of Dr.RIYAS CHUNGATHU done under my supervision in the department of Paediatrics, PSG Institute of Medical Sciences and Research, Coimbatore in fulfilment of the regulations of The Tamil Nadu Dr.MGR Medical university for the award of MD degree in Paediatrics.

DR.A.M.VIJAYALAKSHMI

PROFESSOR AND UNIT CHIEF, PAEDIATRICS

PSG IMS&R, COIMBATORE

ACKNOWLEDGEMENT

At the onset it gives me immense pleasure to express my heartfelt gratitude and sincere thanks to my beloved teacher Dr.A.M.Vijayalakshmi, Professor and Chief unit two, Paediatrics, PSG IMS & R for her constant encouragement and valuable suggestions, without whose help this study would not have been possible.

I am greatly indebted to Dr.Jayavardhana ,Associate Professor , Department of Paediatrics, PSG IMS & R for his guidance in conducting the study.

I extend my heartfelt thanks to Dr.John Mathai Professor and H.O.D Paediatrics,. Dr.Sarah Paul, Dr.Jothilakshmi, Professors, Department of paediatrics, PSG IMS & R for their constant encouragement during the study.

I express my gratitude to Dr.Saravana pandian, ,Dr.Sivanandam,,Dr.Prathiba,Dr.Venkatesh,Dr.Rajesh Assistant Professors, Department of paediatrics, PSG IMS & R for their kind co-operation and support.

I pay my respectful regards to Dr .Marina, Professor, Department of microbiology,for helping me in completion of my thesis.

I sincerely thank Dr.Ramalingam , Principal , PSG IMS & R for his kind cooperation.

I would like to thank my wife Dr.Sumi for her immense support during my study period.

I express my gratitude to Paediatric and Microbiology staffs and secretaries PSG IMS & R for their help during this study

Finally, I thank all my friends and co-postgraduates who supported me during this study.

.

Contents

CERTIFICATE BY THE H.O.D

This is to certify that the thesis entitled "**A STUDY ON THE CLINICAL PROFILE,BLOOD PROFILE AND BLOOD CULTURE SENSITIVITY PATTERN OF SALMONELLA TYPHI IN PAEDIATRIC PATIENTS OF PSGIMS & R"** is the bonafide work of Dr. RIYAS CHUNGATHU done in the department of Paediatrics , PSG Institute of Medical Sciences and Research, Coimbatore under the supervision of Dr.A.M.VIJAYALAKSHMI, Professor and Chief Unit two, Department of Paediatrics in fulfilment of the regulations of the Tamil Nadu Dr.MGR Medical university for the award of MD degree in Paediatrics.

DR.JOHN MATTHAI

PROFESSOR AND HEAD OF PAEDIATRICS

PSG IMS&R, COIMBATORE

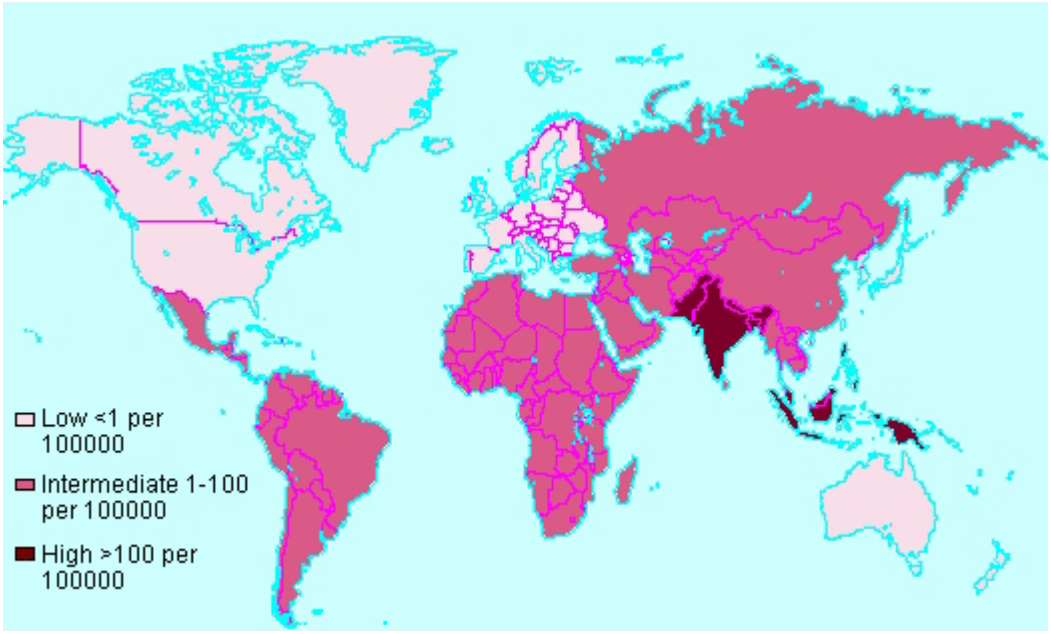
INTRODUCTION

Typhoid fever is a global public health problem,epidemics of typhoid fever and high endemic disease rates have been reported in India and countries in South Asia,however many cases remain undiagnosed and thus the real situation remains unknown.Typhoid fever accounts for an estimated 21 million and 200,000 deaths world wide annually[1] .In 2000 an estimated 5.4 million cases of paratyphoid fever occurred globally.These values are from studies conducted in high incidence areas and therefore not totally unbiased.

In India an estimate of annual typhoid incidence rate of 493.5 cases per 100,000 person years was reported in one study[2]

Typhoid fever has a high social and economic impact as a result of hospitalization of the patients with acute disease or its complications and therefore the loss of income attributable to the duration of the clinical illness.[3]

In areas of endemicity and in large outbreaks,maximum patients were aged between 3 and 19 years.However bacteremic Salmonella typhi infection has been reported in children less than 3 years in India,Bangladesh,Nigeria etc.[4,5]In Indonesia, 900,000 cases per year and over 20,000 deaths are reported to occur.In South America, maximum cases occurred in school going children of 5-19 years and also in adults over 35 years of age.



Annual incidence of typhoid infection worldwide.

Between 1% and 5% of typhoid fever patients are reported to end up as chronic carriers of infection of gall bladder though it does depend on the age,sex and also treatment provided.Chances of ending up as a carrier increases with advancing age and is greater in the female sex.[6]

The Complete blood count in enteric fever is said to be unremarkable.Leukopenia may be seen in 20-25% cases and the differential count demonstrates absolute eosinophilia in 70-80%.However these do not help to differentiate enteric fever from other acute bacterial and viral infections.Thrombocytopenia may be present in 10-15% usually by 2nd week of illness. [7,8,9]

Definitive diagnosis of typhoid fever is by the isolation of S.typhi from blood,bone marrow or a specific anatomical lesion.Blood culture is the mainstay

of diagnosis as more than 80% of the patients with typhoid fever have the causative organism in their blood.[10]Bone marrow aspirate culture is said to be superior than blood culture for the diagnosis as it is positive even in previously treated patients,with long history of illness and for whom there has been a negative blood culture with the recommended volume of blood.[11]

Felix-Widal test is performed on acute serum and measures the agglutinating antibody levels against O and H antigens.The test has only moderate sensitivity and specificity and can be negative in up to 30% of culture proven cases of typhoid fever.This can be attributed to prior antibiotic therapy that has blunted the antibody response.False positivity may arise as Salmonella typhi share O and H antigens with other Salmonella serotypes and has cross reacting epitopes with other enterobacteriacae.In spite of its limitations,the test is extremely useful in developing countries as it is simple,cheap and easily available.[12,13]

Newer diagnostic tools are available now which provide quicker and more reliable diagnoses and could replace Widal test in the future.The Typhidot test developed in Malaysia is performed in just 3 hours and detects specific IgM and IgG antibodies against a 50kD antigen of S.typhi.It has 75% specificity and 95% sensitivity and high negative and positive predictive values.Typhidot-M is specific for IgM antibodies alone.Evaluation of Typhidot and Typhidot-M in

clinical settings showed that they performed better than Widal test and culture method.[14]

IDL Tubex test was developed in Sweden and can detect IgM O9 antibodies within two minutes itself.In a preliminary study involving stored sera the test performed better than Widal test in both sensitivity and specificity.[15] The Dipstick test is a product of Netherlands and is based on the binding of S.typhi specific IgM antibodies in sample to S.typhi lipopolysaccharide (LPS) antigen and the staining of bound antibodie by an anti-human IgM antibody conjugated to colloidal dye particles.[16,17]

Antimicrobial susceptibility testing is crucial for the guidance of clinical management as many isolates are now multidrug resistant [18,19,20] (MDR).Conventionally used drugs like Ampicillin, Chloramphenicol ,Sulfonamide Trimethoprim, Streptomycin and Tetracycline are now resistant.Newer therapy includes fluoroquinolones, 3rd generation cephalosporins,monobactum betalactum (aztreonam) and macrolides(azithromycin). [7,21,22]Reduced susceptibility to fluoroquinolones is indicated by in vitro resistance to nalidixic acid.This is indicated because of the possibility of false in vitro susceptibility against the fluoroquinolone used for treatment. [23,24]The choice of antimicrobial agents for the test is dictated by the agents that are currently used for the treatment and also to prevent the emergence of MDR strains of Salmonella.[25,26]

REVIEW OF LITERATURE

HISTORY[27,28]

The word TYPHOID appears to have its origin from the Greek word "TYPHOS" which means smokes or stupor,sharing its origin with the disease Typhus with which it was once confused.[29]

The first clinical description was given by Thomas Willis in 1659.Budd in 1856 described the transmission of the disease through excreta of patients.Eberth in 1880 described the typhoid bacillus and Gaffky in 1884 isolated it in pure culture.[28]

Salmonella paratyphi A was isolated by Gwyn in 1898 while salmonella paratyphi B was isolated by Achardo and Bensande in 1896 and they also used the term paratyphoid fever.Paratyphi C was isolated by Uhlenhuth and Hubner in 1908.

Widal along with Sicard,introduced the serological agglutination test, now popularly known as the Widal test, in France in the year 1896.Felix and Pitt described the antigen associated with the virulence of the organism and called it Vi antigen.

The first vaccine was prepared by Pfeiffer and Kolle in 1896 in Germany with heat killed organisms.In 1903 Robert Koch outlined three logical methods of typhoid control : disinfect the excreta,improve sewage handling,and isolate

convalescent patient until they become bacillus free.In 1948,Theodore Woodward showed that Chloamphenicol sterilized the blood cultures of typhoid fever patients – thus ushering in the modern era of antibiotics for the treatment of typhoid fever.[27,28]

ETIOLOGY[28]

The causative organism is popularly known as Salmonella typhi.It is strictly S.enteric, subspecies enteric, serotype typhi and is a robust,gram negative bacillus that infects only man and is capable of surviving in hostile environments like ice,water,dust and clothes.[3]

They are gram negative rods of 2-4um x 0.6um in size and are non-acid fast,noncapsulating,non sporing,motile bacilli with peritrichous flagellae.They are aerobic and facultatively anaerobic.They possess 3 important antigens[28,30]:

i.Polysaccharide envelope antigen known as Vi antigen

- Though it has no intrinsic virulence,it appears to confer virulence by masking the oligosaccharide somatic O antigen from immunological attack
- It may act by coating the bacterial surface and prevent the antibacterial and opsonic effect of O antibody
- It is poorly immunogenic, and only low titres of antibody are produced following infection

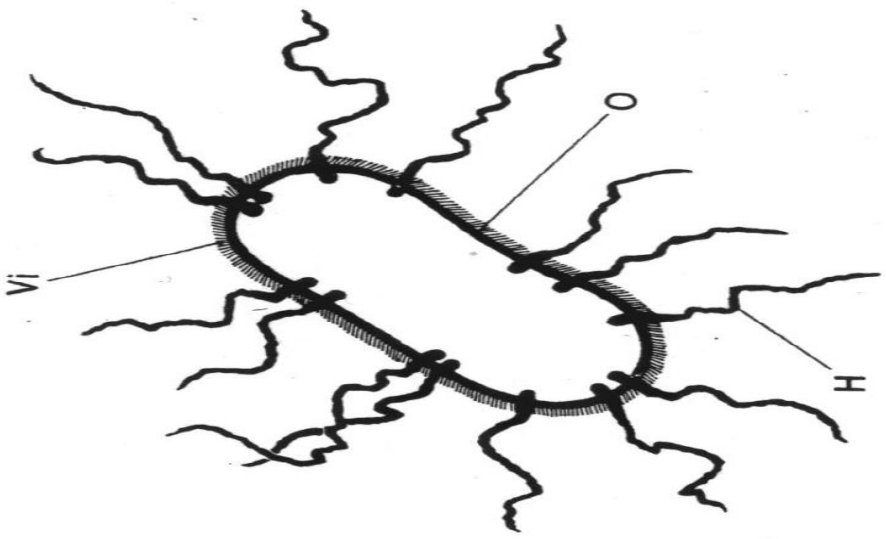
- Its detection is not useful for the diagnosis and hence is not used in Widal test.The persistence of Vi antibody however implies development of carrier state.

ii.Flagellar H antigen

- It is strongly immunogenic and induces antibody formation rapidly and in high titre following infections or immunization
- When mixed with antisera,it agglutinates rapidly to form large, loose, fluffy clumps.

iii.Somatic O antigen

- It forms part of cell wall and is less immunogenic than H antigen,therefore the titre of O antibody induced after an infection or following immunization is lower than that of H antibody
- When mixed with antisera,it forms compact, chalky, granular clumps.



A schematic diagram of a single Salmonella typhi cell showing the locations of the H (flagellar), 0 (somatic), and Vi (K envelope) antigens.

S.typhi can acquire R plasmids which endow it with resistance to chloramphenicol, amoxicillin and cotrimoxazole.A variety of genes (pho P/pho Q, omp R, env Z) have been recently discovered to enable the organisms to adapt to changes in the environment such as shifts of pH,osmolality and calcium concentration and to withstand the effects of microbicidal proteins (defensins) present in the phagosomes of phagocytic cells.

TRANSMISSION[31,32,33]

Mainly by the faeco-oral route and occasionally by the urine-oral route.It may take place directly through soiled hands contaminated with faeces or urine of cases or carriers or indirectly by the ingestion of contaminate water,milk and/or food or through flies.

SOURCE OF INFECTION

It is either the patient or the carriers.Man is the only known reservoir of infection.[1,28,30,31]

1. Cases : A patient with fever (38C and above) that has lasted for at least 3 days,with a laboratory confirmed positive culture (blood,bone marrow,bowel fluid) of S.typhi Carrier : They may be temporary (convalescent/incubatory) or chronic.Patients excrete salmonella in the faeces or urine for about a month.

2. Convalescent carrier : Excrete bacilli for 6-8 weeks after which their numbers diminish rapidly.
3. Chronic carriers : They are those who excrete bacilli for more than one year after a clinical attack.In most,the organisms persist in the gall bladder and bile duct.A chronic carrier state is expected to develop in 2-5% of cases.A famous example is the case of Typhoid Mary,a cook,who gave rise to more than 300 cases in her lifetime. Chronic urinary carrier state is very uncommon and is often associated with some abnormality of the urinary tract.

PATHOGENESIS

The inoculums size required to cause enteric fever is 10^5-10^9 S. typhi organisms.[3]The bacteria invade through Peyer's patches and are transported to intestinal lymph nodes where multiplication takes place within mononuclear cells.Monocytes are unable to destroy the bacilli early in the disease process and so carry these bacilli to mesenteric lymph nodes.From there the bacilli enter the blood stream through the thoracic duct causing a transient bacteremia.These circulating bacilli then reach the reticuloendothelial cells in the liver,spleen and bone marrow and may seed other organs.After proliferation there,bacteremia recurs.The gall bladder is particularly susceptible to infection and local

multiplication occurs there and produces large number of bacilli which reach the intestine through the bile.[33-36]

In carriers,large number of virulent bacilli pass to the intestine daily and are excreted in stool,without entering the epithelium of the host.

CLINICAL FEATURES[27,30,31,35,36]

"A case of typhoid fever may present as a disease,clinically indistinguishable from malaria,progress to bacillary dysentery,mimic a case of acute bronchitis,stimulate a fully fledged case of lobar pneumonina,cause an acute abdomen in perforation and then finally,with its evil spent,linger on as an orchitis,myocarditis or a peripheral neuritis."

The above quote gives an idea of the varied presentation of enteric fever.Variation of clinical features may depend upon the age, race, religion, socioeconomic status, season, sanitation and nutrition.

Season – Higher incidence is seen in monsoon – from June to October,mainly because of contamination of food by flies.

Sex – Equal incidence is noted in many studies whereas in others there is a greater incidence in males.Carrier rate is more in females.

Age- Incidence is maximum in adolescents and young adults.After the age of 20,the incidence falls probably due to acquisition of immunity from

clinical and subclinical infection.The clinical picture in infants and young children is non specific, varies significantly and the disease is severe and takes longer time for recovery.The clinical profile in older children and adolescents is similar to that in adults.A study by Sinha A,Sazawal S,Kumar R et al in 1999 concluded that typhoid is a significant cause of morbidity between 1 and 5 years of age.[4]

Mode of onset – It could be typical,as seen frequently in older children and adults,or atypical,as seen more in infancy and childhood.

Typical onset: It is normally insidious with malaise as a vague but typical presenting symptom.Chills are common though rigors are not.They usually have headache which is nagging and persistent.Generalised aching in muscles and joints,abdominal pain,diarrhea more common than constipation are some other features.Cough,sore throat and poor appetite with a generalized feeling of unwellness are also seen.

Atypical presentation : Here the onset may be abrupt with the patient worsening considerably within a day or two with symptoms suggesting septicemia due to streptococci and pneumococci.Pneumo-typhoid is when patient has acute lobar pneumonia and S.typhi may be isolated from the sputum.Sometimes mental symptoms like states of confusion, stupor, psychosis or even coma may dominate.Typhoid nephritis is rare with urinary symptoms,renal pain and hematuria.Abdominal pain may be severe enough to

suspect appendicitis,when a leucocye count may help to distinguish.Gall bladder pain is more common in convalescence.Jaundice is rare but cases have been reported with jaundice presenting in first week and associated with hematuria and other forms of hemorrhage.Early presentation of symptoms of acute peritonitis,due to perforation of intestine is also uncommonly seen.

Ambulant or latent form – Seen in children with insidious onset when they present with complications like convulsions, delirium or signs of intestinal perforation or hemorrhage.

Fever : Studies show that 60% have continuous fever while the rest may have intermittent,remittent or irregular fever.Chills is common whereas rigors is not.Step ladder pattern of fever is classically described in typhoid and is one which climbs by about 2°F in the evening and falls 1°F in the morning so that by the end of 5 days it has reached a plateau of between 102-104°F above which it rarely descends.However this pattern is rarely seen in children.[37,38]

Other clinical signs include expressionless appearance of the patient,delirium,coated tongue that spares the tips and edges,disended abdomen,mild hepatosplenomegaly and presence of coarse crepitations and rhonchi on auscultation.Relative bradycardia may occur in less than half of the patients.[39]

The characteristic rose spots are rashes that appear in crops from 7th to 10th day,first upon the abdomen and then on the thorax and extremities.They are flattened papules that disappear on pressure with diameter of 2-4mm.After persisting for 2-3 days they disappear leaving a brownish stain.They are also present in the typical relapse.On the Indian skin however such spots are not easily recognized.

Complications usually arise in the second week.[37,38]By the third week,patient may lapse into the typhoid state where he may be disoriented and toxemic,sleepless,confused and muttering and is also called "muttering delirium or coma vigil".Pulse may become thread,respiration shallow and rapid.Expressionless face known as Hippocrates facies reflects profound toxemia.Payers patches may become necrotic and ulcerative and bleeding or perforation may occur.At this stage the so called "pea soup diarrhea" may appear.

Death may occur from overwhelming toxemia, myocarditis, intestinal hemorrhage or perforation.[18,20,40]

Those who survive into the 4th week may show an improvement of symptoms and signs but intestinal complications may occur and convalescence prolonged.This is the week of convalescence.

COMPLICATIONS: [20,41,42]

i) GASTROINTESTINAL COMPLICATIONS

- Intestinal Hemorrhage
- Intestinal perforation
- Paralytic ileus or meteorism

2) HEPATOBILIARY COMPLICATIONS[41,42]

- Acute cholecystitis
- Chronic cholecystitis and carrier state

3) CENTRAL NERVOUS SYSTEM COMPLICATIONS[42,43]

- Neuropsychiatric complications
- Typhoid meningitis

4) HEMATOLOGICAL COMPLICATIONS[7,8]

- Anemia
- Leucopenia/ Leucocytosis
- Hemolytic anemia
- Disseminated Intravascular Coagulation

5) RESPIRATORY COMPLICATIONS

- Bronchitis
- Typhoid pneumonia
- Laryngitis
- Acute Respiratory Distress Syndrome

6) CARDIOVASCULAR COMPLICATIONS

- Myocarditis[42,43]
- Venous thrombosis

7) MUSCULOSKELETAL COMPLICATIONS

- Periostitis of tibia or ribs
- Typhoid arthritis
- Typhoid osteomyelitis – more common in patients with sickle cell disease
- Abscess formation in bones

8) GENITOURINARY COMPLICATIONS

- Renal failure
- Nephritic syndrome
- Suppurative typhoid pyelonephritis
- Typhoid cystitis
- Typhoid orchitis

9) POST TYPHOID ANHIDROSIS

10) ABSCESS FORMATION – commonest is pelvis abscess.

11) MISCELLANEOUS

- Parotitis
- Pancreatitis
- Thyroiditis

DIFFERENTIAL DIAGNOSES[31,36,38]

- Malaria
- Miliary tuberculosis
- Hepatitis
- Leptospirosis
- Rickettsial diseases
- Tularemia
- CMV infections
- Lymphomas
- Vasculitis

DIAGNOSTIC INVESTIGATIONS[44]

Diagnostic test	Sensitivity range (%)	Sensitivity range (%)	Comments
Microbiological tests			
Blood culture	40-80	NA	Widely regarded as the gold standard, but sensitivity may be low in endemic areas with high rates of antibiotic use—hence

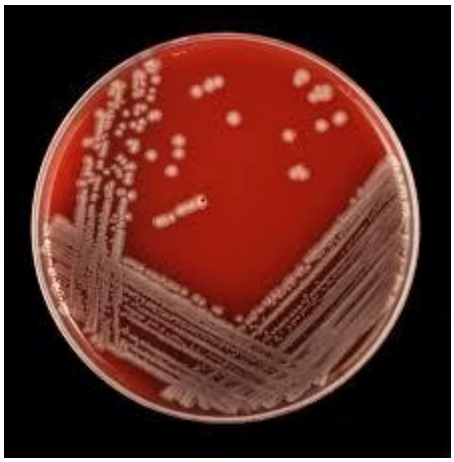
			true specificity is difficult to estimate
Bone marrow culture	55-67	30	Greater sensitivity but invasive and thus of limited clinical value, especially in ambulatory management
Urine culture	0-58	NA	Variable sensitivity
Stool culture	30	NA	Sensitivity lower in developing countries and not used routinely for follow-up
Molecular diagnostics			
Polymerase chain reaction	100	100	Promising, but initial reports indicated similar sensitivity to blood cultures and lower specificity
Nested polymerase chain reaction	100	100	Promising and may replace blood culture as the new "gold standard

Serological diagnosis			
Widal test (tube dilution and slide Agglutination)	47-77	50-92	Classic and inexpensive. Despite mixed results in endemic areas, still performs well for screening large volumes. May need standardisation and quality assurance of reagents
Typhidot	66-88	75-91	Lower sensitivity than Typhidot-M
Typhidot-M	73-95	68-95	Higher sensitivity and specificity than classic Typhidot in some series, but other evaluations suggest that the performance may not be as robust in community settings as in hospital

Tubex	65-88	63-89	Promising initial results but has yet to be evaluated in larger trials in community settings
Others			
Urine antigen detection	65-95	NA	Preliminary data only

MICROBIOLOGICAL TESTS

1) **BLOOD CULTURE** : S.typhi is cultured from venous blood in 90% of the cases during the first 10 days of the disease.Sensitivity reduces to 50% by 3rd week.Addition of Ioquoid (sodium polyanethol sulfonate) counteracts the bactericidal action of blood.[1,28,31,32,33,45]



CLOT CULTURE : Here the blood collected is allowed to clot before culturing as the bactericidal property of blood seems to be concentrated

mainly in the serum.Therefore clot culture may be positive in cases where the blood culture is negative.Sensitivity is 69-84%.[11,28]

2) **BONE MARROW CULTURE** : It is more specific than blood culture as the organisms can live after it has left the blood stream especially in those who are treated with antibiotics.It is used to find the antibiotic sensitivity or phage type of a strain causing outbreak.[46]It is indicated in prolonged febrile illness of unknown origin and in those with severe prolonged neutropenia.However its invasive nature does not make it the gold standard.[45]

3) **STOOL CULTURE** : Its positivity increases more in the 3rd week as compared to the 1st.It is taken from a properly sterilized bed pan in a special container.Rectal swabs are not useful in diagnosis.Successful culture depends on the use of enrichment media like McConkey and Wilson Blair media,as the salmonella are greatly outnumbered in the faeces by normal flora.Carriers may also demonstrate a positive culture.

4) **URINE CULTURE** : It is positive in a quarter to one third of the cases but there seems to be no regular excretion pattern as in faeces[47].Bacteruria is usually temporary but if it persists and person becomes a urinary carrier,then a preceding urinary tract abnormality should be suspected.[28,31,45]

5) **BILE CULTURE** : It may give positive results more than blood and is especially reliable in determination of carrier state.A convenient method is by string capsule devise or duodenal intubation during endoscopy.[31,45]

6) **ROSE SPOTS CULTURE** : Since the occur as the result of embolisation of bacteria,skin snips can be cultured especially in patients who have take antibiotics.[31,46]

7) **MISCELLANEOUS** : S.typhi has been isolated from cerebrospinal fluid, peritoneal fluid, mesenteric lymphnodes, pharynx, tonsils and abscesses.[28,31,42]

Antimicrobial susceptibility testing is crucial for the guidance of clinical management as many isolates are now multidrug resistant [18,19,20] (MDR).Conventionally used drugs like Ampicillin, Chloramphenicol ,Sulfonamide Trimethoprim, Streptomycin and Tetracycline are now resistant.Newer therapy includes fluoroquinolones, 3rd generation cephalosporins,monobactum beta lactum (aztreonam) and macrolides(azithromycin). [7,21,22] Reduced susceptibility to fluoroquinolones is indicated by in vitro resistance to nalidixic acid.This is indicated because of the possibility of false in vitro susceptibility against the fluoroquinolone used for treatment. [23,24]The choice of antimicrobial agents for the test is dictated by the agents that are currently used for the treatment and also to prevent the emergence of MDR strains of Salmonella.[25,26.]In vitro susceptibility testing usually involves disc diffusion.

BACTERIOPHAGE TYPING : This is especially important in epidemiological differentiation of organisms producing outbreaks and for the identification of the source.[28,31,42]

SEROLOGICAL TESTS

1)WIDAL TEST : This test measures the H (flagellar) and O (osmotic) agglutinins for typhoid and paratyphoid bacilli in patient's sera.By the end of first week of illness the antibodies tend to appear and show progressive rise in the titers as the disease advances.[1,9,12,13,40]

PRINCIPLE: Agglutinins against H (flagellar) and O (somatic) antigens of Salmonella group of organisms were detected quantitatively employing killed suspension of appropriate organisms.

PROCEDURE:

1.For each test sample, arrange four rows of 6 tubes in a rack.

2.Prepare master dilutions by taking 5 tubes in another rack,place 7ml of normal saline in the first tube and 3.5ml in the remaining 4 tubes.Add 0.5ml of serum to the first tube and mix well.Transfer 3.5ml from the first tube to the next tube and mix well.Continue successive transfer of 3.5ml quantities till the last tube is reached.This will give final dilution of 1:30, 1:60, 1:120, 1:240 and 1:480 after the addition of antigen in step 4.[9,28]

3.Transfer 0.5ml quantities from the master dilution tubes to each tube of the corresponding vertical row in test rack.Place 0.5ml of normal saline in each of the tubes in the last i.e. 6^{th} row to serve as controls.

4.To each of the 6 tubes in the first 4 horizontal rows,add 0.5ml of Salmonella typhi O, S. typhi H, S.paratyphi A (H) and S.paratyphi B (H) antigens respectively.

5.Shake the rack well to mix and incubate at 37°C overnight.

6.Note the highest dilution in which there is evidence of agglutination as observed by the naked eye.With H antigens the agglutination is floccular cotton wool type and with O antigens it is fine granular and appears as granular matt at the bottom of the tube.

INTERPRETATION:

1..The agglutination titer will depend on the stage of disease.Agglutins will usually appear by the end of the first week,so that blood taken earlier may give a negative result.The titer increases steadily till the third or fourth week after which it declines gradually.[28]

2.Agglutination titers of TO=1:80 are significant and the rise in titers after repetition of the Widal test after a few day will confirm enteric fever diagnosis.

3.Agglutination titers of TH=1:160 and above are typically found in cases of enteric fever.

4.Those with history of prior infection or immunization may develop an anamnestic response during an unrelated fever.This may be differentiated by repetition of Widal test after a week.The anamnestic response shows only a transient rise,while in enteric fever the rise is sustained.

5.A moderate rise in the titer of all the H agglutinins simultaneously against all H antigens is suggestive of a recent TAB vaccination.

2)TYPHIDOT

It is an enzyme immunoassay that detects IgG and IgM antibodies against a 50KD outer membrane protein distinct from the somatic (O), flagellar (H) or capsular (Vi) antigen of Salmonella typhi.IgM detection reveals acute typhoid in the early phase of infection,while the detection of both IgG and IgM suggests acute typhoid in the middle phase of infection.In areas of high endemicity where the rate of typhoid transmission is high the detection of specific IgG increase.[1,9] Typhidot-M detects specific IgM antibodies only.

3)ENZYME LINKED IMMUNOSORBENT ASSAY (ELISA)

It is used to detect Vi antigens in the urine of patients.Vi antibodies typically rise after 3-4 weeks of illness and are of less value in the early diagnosis of the

illness.It can be done in polystyrene tubes (Macro ELISA) or poly vinyl microtitre plates (Micro ELISA).[6,9,32]

4)TUBEX TEST

It is based on detecting antibodies to a single antigen in S.typhi only.The 09 antigen used in this test is very specific,found in only sero group D salmonellae.A positive result always suggest a salmonellae infection but not which group D salmonella is responsible.Infection by other serotypes like S. paratyphi A give negative result.It detects IgM antibodies and so is useful in diagnosis of current infections.[1,9]

5)IgM DIPSTICK TEST

This test is based on the binding of S.typhi specific Ig antibodies to S.typhi lipopolysaccharide (LPS) antigen and the staining of bound antibodies by an antihuman IgM antibody conjugated to colloidal dye particles.It is useful in places where culture facilities are not available as it can be performed without formal training and in the absence of specialized equipments.The sensitivity of this test increases with time.[1,9,28]

6)COUNTER IMMUNOELECTROPHORESIS (CIE)

It is done using veronal buffer extract and detects the lipopolysaccharide and surface protein antigens of S.typhi.It is more reliable and specific for serological

diagnosis of typhoid fever than Widal but they have the same disadvantages as Widal.[1,9]

MOLECULAR DIAGNOSTICS

1)POLYMERASE CHAIN REACTION

PCR methods targeting the flagellin gene,somatic gene, Vi antigen gene, 5S-23S spacer region of the ribosomal RNA gene, INVA gene, flic gene, Hi1 A gene of Salmonella typhi for diagnosis of typhoid fever have been evaluated with excellent sensitivity and specificity compared to positive (blood culture proven) and healthy controls.The turn-around time for diagnosis has been less than 24hr.A disadvantage is that the result in those with past history of typhoid,carrier,those vaccinated and are culture negative but yielding a PCR positive result may in fact be false positives.It is also costly and requires sophisticated instruments.[1,9,28,49]

MISCELLANEOUS INVESTIGATIONS[31,32,33,35,36]:

1) Hemoglobin – May be low and the most common anemia encountered is mild normocytic normochromic anemia.
2) WBCs – Leucopenia of 3000-4000 cells is characteristic of the febrile phase of enteric fever.A sudden increase in count to 10,000 cells/cumm or higher should suggest the possibility of intestinal

perforation,hemorrhage or a pyogenic complication. Eosinopenia may be seen due to trapping of eosinophils in reticuloendothelial system.[9]

3) Platelets – Thrombocytopenia may be seen.[9]
4) ESR – is usually elevated.
5) Urine routine – Hematuria and proteinuria with casts may be seen in cases of Nephrotyphoid.
6) Chest Xray – features of typhoid pneumonia or ARDS
7) USG Abdomen – features of silent perforation or pelvic abscess formation
8) DIC profile – PT, PTTK, serum fibrinogen and FDP levels may be elevated secondary to typhoid hepatitis and/ or septicemia.
9) Serum electrolytes and arterial blood gases – hypokalemia and hyponatremia may be seen.
10) Renal function tests – Acute renal failure may be seen in peripheral circulatory shock (due to septicemia or myocarditis) and typhoid nephritis.
11) Bone marrow – this is evaluated in patients with prolonged pancytopenia and for culture when the diagnosis is in doubt.
12) Adenosine deaminase enzyme (ADA)- is raised in typhoid though it is not specific.

TREATMENT

Both general and specific measures play important roles in the treatment of typhoid fever.

By general measures we mean adequate hydration and nutrition, antipyretics, prevention and control of spread. Specific measures implies the use of antibiotics.

Antibiotic therapy

Conventionally used drugs like Ampicillin, Chloramphenicol ,Sulfonamide Trimethoprim, Streptomycin and Tetracycline are now resistant.However due to change in sensitivity and the pattern of bacterial infection,wide spread occurrence of multi drug resistant typhoid fever has been reported from South East Asia and Indian subcontinent.Newer therapy includes fluoroquinolones (ciprofloxacin,ofloxacin,pefloxacin etc.), 3rd generation cephalosporins (eg. Ceftriaxone,cefotaxime, ceftazidime, cefoperazone),monobactum beta lactum (aztreonam) and macrolides(azithromycin). [7,21,22]

In randomized controlled trials involving patients infected with quinolone-susceptible S.enterica serotype typhi,quinolones have proved safe in all age groups and are rapidly effective even with short course of treatment (3-7 days).Cure rates exceed 96% and less than 2 percent of treated patients have

persistent fecal carriage or relapse.[50] On routine drug sensitivity testing some strains of S.typhi may show susceptibility to fluoroquinolones but show poor clinical response on actual treatment.However these same strains may show resistance to nalidixic acid on sensitivity testing.Therefore if the isolate shows resistance to nalidixic acid then it implies a higher MIC for fluoroquinolones and thus higher doses of fluoroquinolones are required for effective treatment. Patients with enteric fever due to isolates with decreased ciprofloxacin susceptibility are more likely to have prolonged fever clearance times and higher rates of treatment failure .[24,25,51]

Since the clinical cure rate reported with Ceftriaxone,the most commonly used 3rd generation cephalosporin for typhoid, is above 90% according to various authors,it is being given commonly for typhoid.However many are of the opinion that it is better to give them as first line only for complicated cases.Ceftriaxone is also known to keep the relapse rate lower and prevent carrier state.[52]

Chowta MN,Chowta NK conducted a retrospective study on clinical profile and antibiotic sensitivity in 1999-2001 and concluded that resistance of Salmonella typhi to Amoxicillin, Ampicillin, Chloramphenicol and Cotrimoxazole were significantly high.Ciprofloxacin showed resistance of 18% and Cephalosporins were 100% sensitive. [53]

Yaramis A,Yildirim I,Katar S et al conducted a study on 314 children admitted to the Dicle University Hospital and revealed resistance rates of 17% for Ampicillin,5% for trimethoprim-sulfamethoxazole,4% for ceftriaxone and 6% for sulbactam-ampicillin.No resistance was detected against quinolones and chloramphenicol.[54]

Jog S,Soman R,Singhal T et al conducted a retrospective chart review on enteric fever in a hospital in Mumbai and concluded that there was a high culture positivity despite receipt of prior antibiotics,high prevalence of nalidixic acid resistance (79%),return of susceptibility to chloramphenicol (96%),100% sensitivity to ceftriaxone and non superiority of combination therapy versus single agent therapy.[55]

Walia M,Gaind R et al undertook a retrospective analysis of blood culture-confirmed cases of enteric fever diagnosed at Safdarjang Hospital, New Delhi, India from 2001-2003 and concluded that there was a significant decline in MDRS from 21.9% in 2001 to 12.4% in 2003 with a significant increase in nalidixic acid-resistant Salmonella (NARS) from 56.9% in 2001 to 88.9% in 2003 . Minimal inhibitory concentrations (MICs) of ciprofloxacin for NARS were increased but were within National Committee for Clinical Laboratory Standards susceptibility ranges. [56]

A prospective randomized controlled parallel study was conducted in 2007 by Kumar R,Gupta N and Shalini on 93 children of age upto 12 years with blood culture proven S.typhi to evaluate multi drug resistant typhoid fever and therapeutic response of ofloxacin and ceftriaxone.Those children treated with ceftriaxone had a shorter time to defervescence compared to ofloxacin with a mean of 4.258 and 4.968 respectively.[24]

Frenck RW Jr.,Mansour A,Nakhla I et al conducted a study in Cairo on 149 children and adolescents between 3 and 17 years age with clinical typhoid.They were treated with either oral Azithromycin or intravenous Ceftriaxone daily for 5 days.Cure was achieved in 94% of patients treated with Azithromycin and 97% of patients treated with Ceftriaxone.Azithromycin group took longer time to clear bacteremia and had no case of relapse when compared with the Cefriaxone group.They concluded that a 5 days course of Azithromycin is an effective treatment for uncomplicated typhoid fever in children and adolescents.[57]

Butler T,Sridhar CB,Daga MK et al conducted a randomized open trial in 4 hospitals in India on Azithromycin versus Chloramphenicol for treatment of enteric fever.The results indicated that azithromycin given once daily for 7 days was effective therapy for typhoid fever in a region endemic with chloramphenicol- resistant S.typhi infection and was equivalent in effectiveness

to chloramphenicol given to patients with chloramphenicol-susceptible infections.[58]

Treatment of carriers

Amoxicillin in the dose of 100mg/kg in three divided doses daily for 3 months or Trimethoprim-Sulfamethoxazole for 3 months or Ciprofloxacin for four weeks have cure rates of more than 80%.The high concentrations of amoxicillin and fluoroquinolones in bile and the superior intracellular penetration of fluoroquinolones put them at an advantage compared to trimethoprim-sulfamethoxazole.In cases of combined anatomic abnormalities,surgery also is required for eradication.Those with urinary carriage associated with schistosomiasis haematobium have to be treated with praziquantel also.To be considered a non-carrier,stool cultures are to be repeated weekly till 3 consecutive negative cultures are obtained.[59]

Prevention and control[28,31,33]

There are 3 steps of defence against typhoid:

- Limit the infectivity of sources
- Prevent transmission of disease
- Immunization

Limit the infectivity of cases and carriers by early diagnosis,isolation, adequate treatment and disinfection and then proper follow up.[28,32,33]

The cases and carriers should not be allowed to handle food and water for others.Proper health education has an important role as something as simple as washing hands with soap may come a long way in prevention of spread of the disease.Improvement in basic sanitation is a must.[33]

Immunization [33,59]

It is the only specific preventive measure though it does not give 100% protection,it definitely lowers the incidence and morbidity.It is recommended in endemic areas and those travelling to endemic areas,household contacts of carriers,groups at risk like school going children and laboratory workers.[9,33]

Heat killed whole organisms S.typhi has been the mainstay of treatment for long.

Heat phenol inactivated vaccine manufactured by Wyeth (TAB) is given as two 0.25ml subcutaneous injections separated by more than 4 weeks for children older than 6 months to 10 years of age.For those older than 10 years 0.5ml injections are given.Booster doses have to be given every 3 years.In India,a divalent typhoid-paratyphoid A vaccine or the monovalent typhoid vaccine is preferred.[33,59]

Acetone inactivated vaccine is preferred in endemic areas as they have higher efficacy due to preservation of Vi antigen in this preparation.However it

is expensive and has more side effects.It is only available to US military personnel[33].

Typhoral or live attenuated oral vaccine Ty21a is given in the form of an enteric coated capsule.4 doses are given 1 hour before meal with cool liquid on alternate days.Not recommended for children less than 6 years,the immunosuppressed and those on antibiotic therapy especially sulphonamides and antimalarial mefloquine therapy.Booster may be given after 3 years.

A caspsular polysaccharide vaccine ViCPS (TyphimVi) is given as a single 0.5ml dose intramuscularly.Booster every 2 years.Not recommended in children less than 2 years of age.

A recently introduced conjugate Vi vaccine formed by fusion of the Vi polysaccharide to a non-toxic recombinant Pseudomonas aeruginosa exotoxin A (Vi-r EPA) is given in a two dose regimen to children between 2 and 5 years of age.It also has the potential to be immunogenic in children aged less than 2 years and therefore may be incorporated into the WHO extended programme on immunization in endemic areas.However it is not commercially available at present[59].

In 2003,a randomized controlled study conducted by Saha MR,Dutta P,Patil A et al on susceptible age group for typhoid fever with Vi antigen vaccine and Ty21a vaccine proposed to immunize younger children less than 3

years in first phase to arrest infection and advocated the administration of subsequent booster dose in potentially endemic population.[5]

The clinical profile and blood picture is changing nowadays because of the emergence of multiresistant strains.Appropriate antibiotic treatment is critical to curing typhoid with minimal complications.This in turn makes the prognosis better. Such a study hopes to find the new trends in clinical profile and blood picture in the local population and also which antibiotics are more useful in cases of enteric fever at the moment & thus better the prognosis.

AIM OF THE STUDY

Primary Aim:

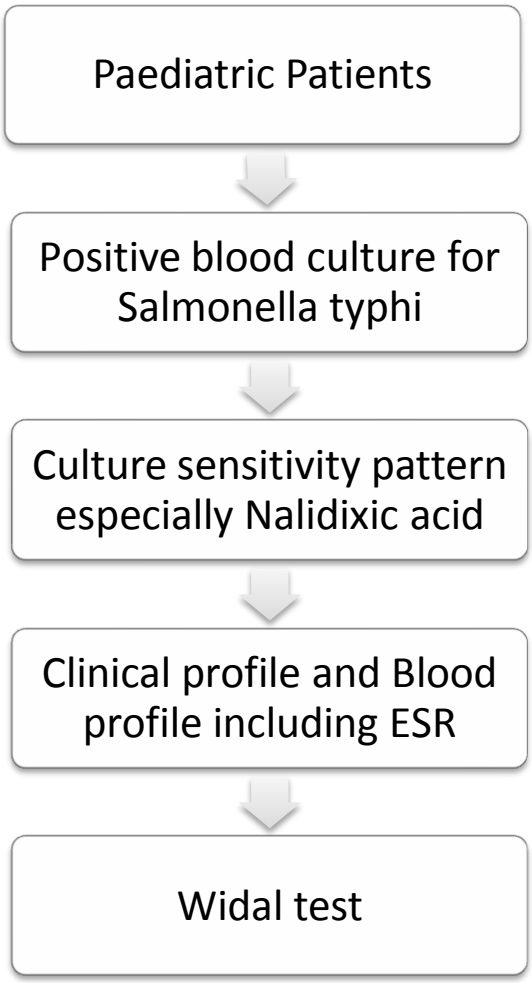
To determine the blood profile and blood culture sensitivity of Salmonella typhi and comparison of Widal with blood culture in Paediatric patients of PSG IMS & R

Secondary Aim:

To assess the microbiological profile of Salmonella typhi especially with reference to Nalidixic acid

MATERIALS AND METHODS

- This is a retrospective observational study conducted among : Inpatients and outpatients of department of Paediatrics of PSG IMSR with confirmed diagnosis of Salmonella typhi including locales in and around Coimbatore including referred cases.Case records from January 2009 to December 2012 were collected and analysed.
- It is a cross-sectional,hospital based study spanning over a period of 18 months from June 2011 to November 2012.
- Study Design



- Inclusion criteria included

  Children ≤15 yrs with Blood Culture Positive for Salmonella typhi of both sexes.

- Exclusion criteria included

  Immunocompromised children

- Case sheets of 50 patients, from January 2009 to December 2012,fitting into the inclusion and exclusion criteria were selected .
- Several data were collected including Clinical features, Culture sensitivity pattern,blood analysis including ESR and Widal test.
- Blood culture was performed by collecting 5cc venous blood and diluting it 4 times under normal circumstances and 10 times if treated with antibiotics,and then injecting into a bulb containing 20-30cc of 5% bile broth.The bulb is incubated for 24-48 hrs ar 37°C and subcultures are made on McConkey's medium.Cultures are declared negative after incubation for 10 days.
- Antibiotic sensitivity pattern was assessed by the Kirby-Bauer disc diffusion method where discs containing antibiotics are placed onto an agar plate upon which bacteria are growing. If the bacteria are sensitive to the antibiotic,a zone of inhibition is seen around the disc.
- Widal test was done by adding 0.5ml of Salmonella typhi O,Salmonella typhi H,Salmonella paratyphi A(H) and Salmonella paratyphi B(H) antigens respectively to test tubes with diluted sera of

1:30,1:60,1:120,1:240 and 1:480 concentration and also control of 0.5ml normal saline.After shaking the rack well,it is incubated at 37°C overnight.Then with naked eye,the highest dilution in which there is evidence of agglutination is noted.

- Temperature was recorded using mercury/ digital thermometer and noting the axillary reading in °F.

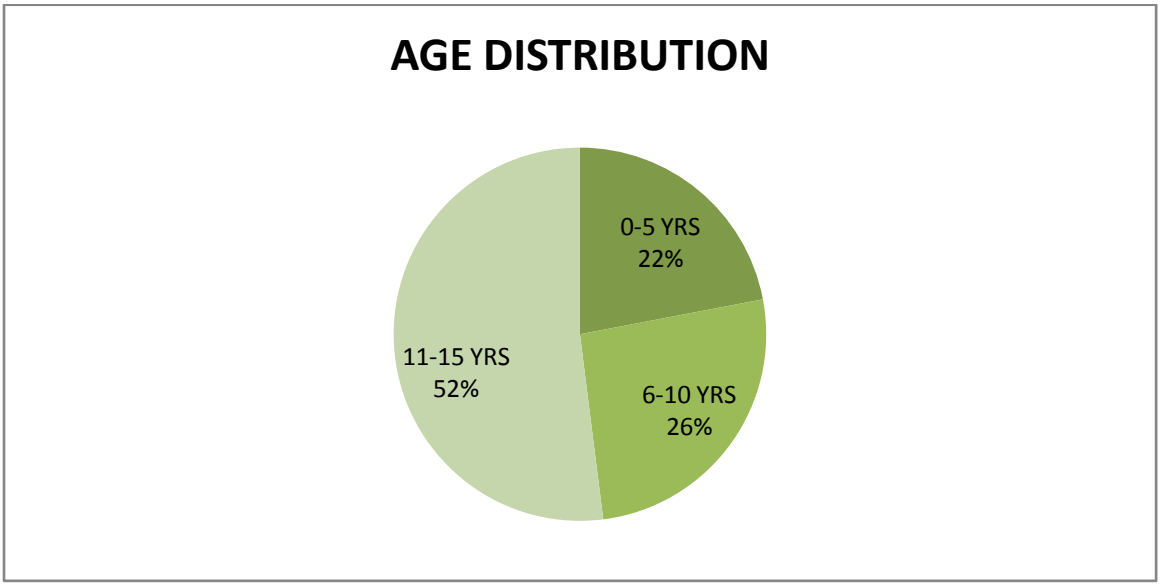
• The data collected was then analysed using mainly Descriptive statistics and Chi square analysis

OBSERVATION AND RESULT

86 cases records of patients treated as Typhoid fever were selected.Of them 36 cases were discarded if blood culture was either not done or were negative, or were partially treated cases.All cases of paratyphoid infection were also discarded.Thus 50 cases with blood culture positive for Salmonella typhi were chosen and data collected and analysed.The observations were as follows.

AGE DISTRIBUTION

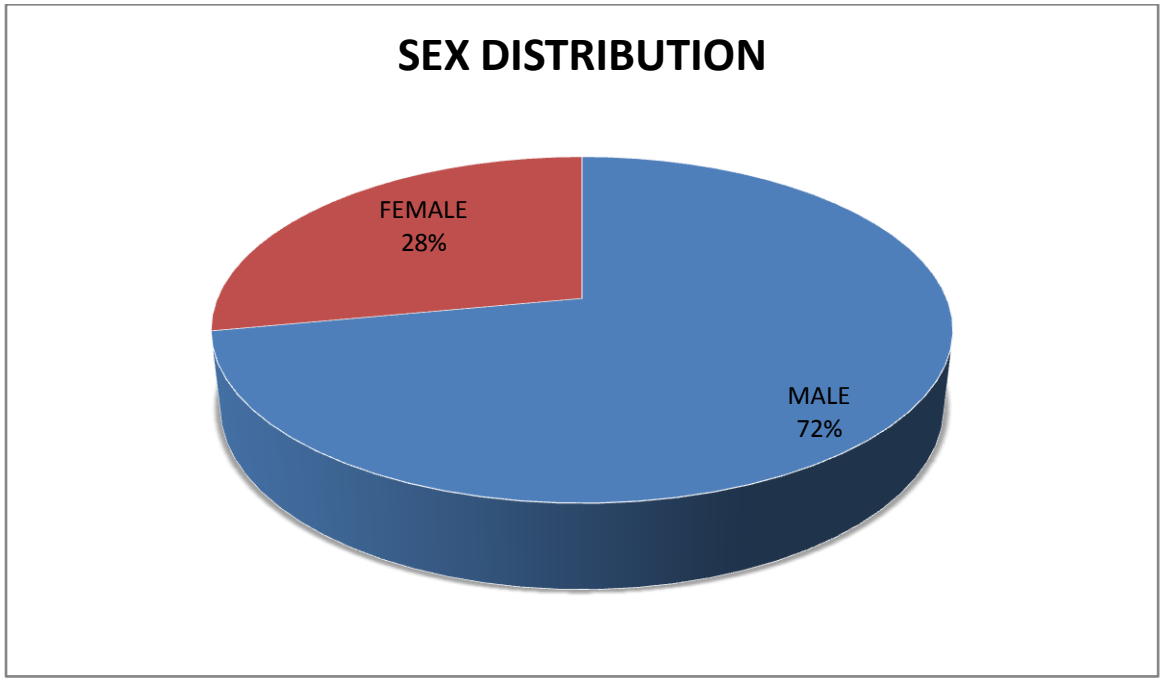
AGE IN YEARS	NO. OF CASES (n=50)S	PERCENTAGE (%)
0-5	11	22
6- 10	13	26
11-15	26	52
TOTAL	50	100



Of the 50 cases included in the study,a majority of 26 cases (52%) fell in the age group of 11-15 years.13 cases or 26% were of the 6-10 years age group and 11 cases or 22% were of the 0-5 years age group.Therefore maximum cases were of the school going age group and implies the importance of preventing typhoid fever in that group by immunization.

SEX DISTRIBUTION

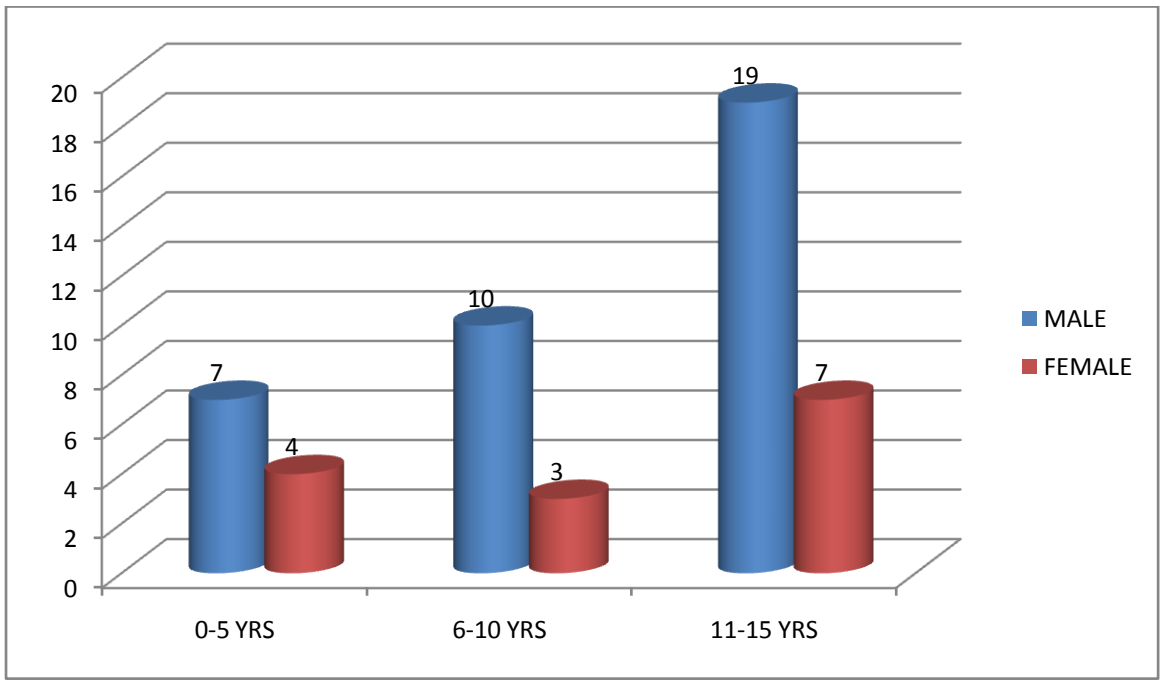
SEX	NO. OF CASES (n=50)	PERCENTAGE (%)
MALE	36	72
FEMALE	14	28
TOTAL	50	100



In our study,36 cases or 72% of the cases were males and only 14 cases or 28% were females.Thus it is more common among males.

AGE WITH SEX DISTRIBUTION

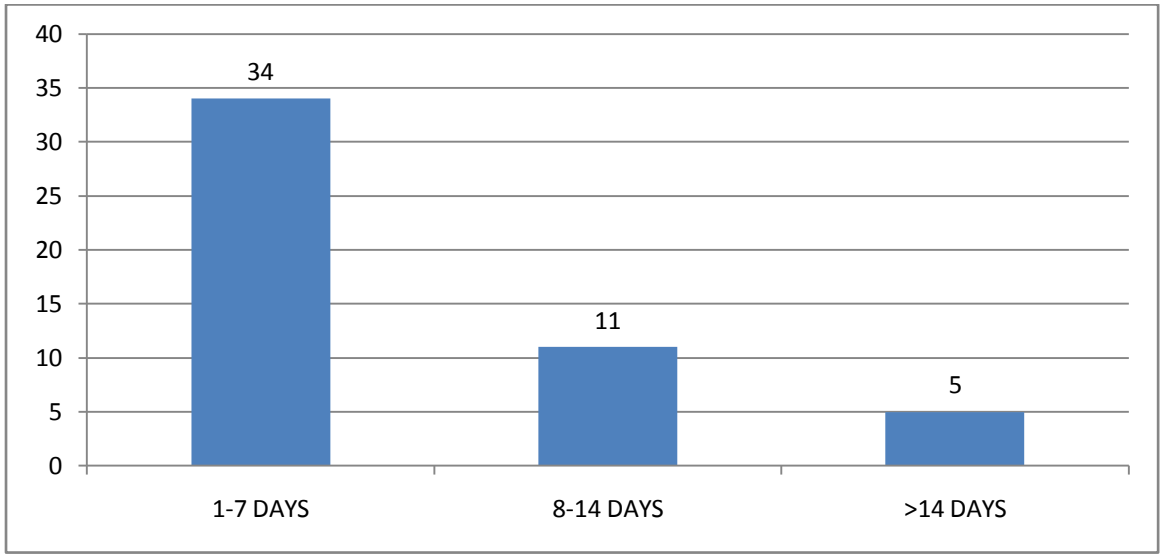
AGE IN YEARS (n=50)	MALE	FEMALE	TOTAL
0 – 5	7	4	11
6 – 10	10	3	13
11 - 15	19	7	26
TOTAL	36	14	50



Out of the 50 cases included in the study, majority or 26 of the cases were of the age group 11-15 years and of them 19 were male and only 7 were female.In all 3 selected age groups,males were the majority.

DURATION OF FEVER

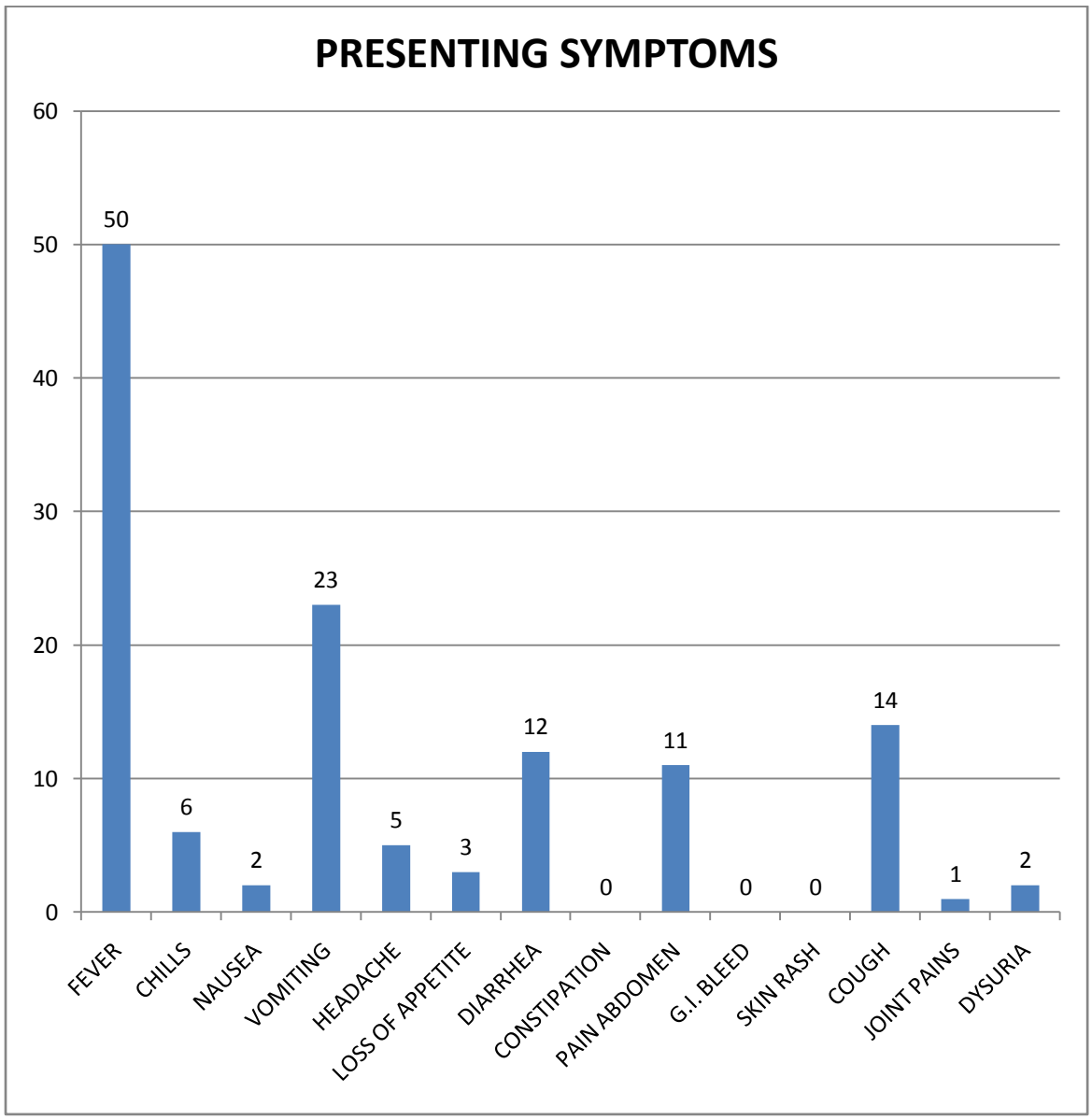
DURATION OF FEVER IN DAYS	NO. OF CASES (n=50)	PERCENTAGE (%)
1-7	34	68
8-14	11	22
>14	5	10
TOTAL	50	100



34 of the 50 cases ie 68% had fever of 1-7 days.Only 5 cases or 10% had fever of more than 2 weeks duration.11 cases or 22% had fever of 8-14 days duration.

PRESENTING SYMPTOMS

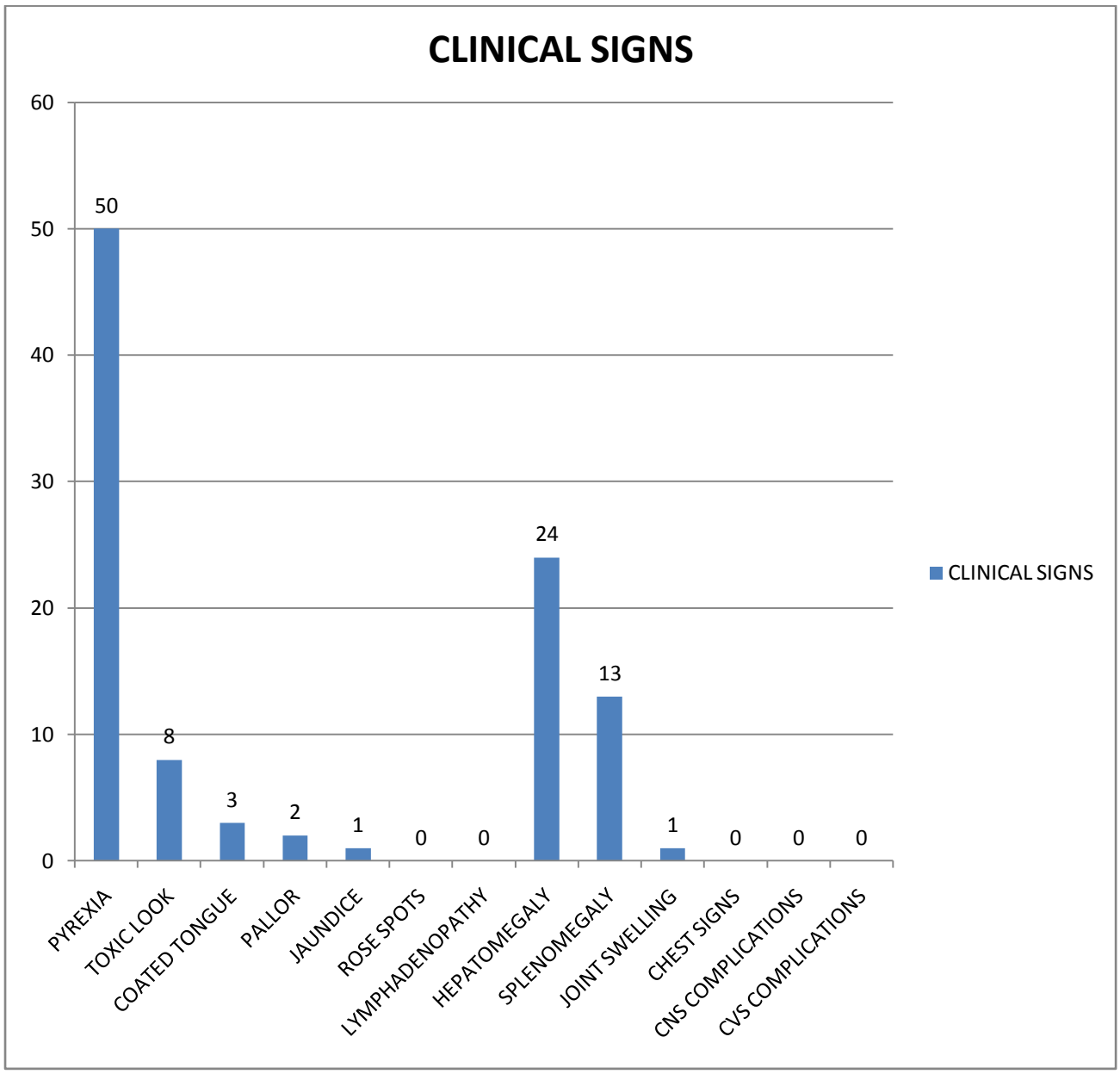
SL. NO.	SYMPTOMS	NO. OF CASES (n=50)	PERCENTAGE (%)
1	FEVER	50	100
2	CHILLS	6	12
3	NAUSEA	2	4
4	VOMITING	23	46
5	HEADACHE	5	10
6	LOSS OF APPETITE	3	6
7	DIARRHEA	12	24
8	CONSTIPATION	0	0
9	PAIN ABDOMEN	11	22
10	G.I. BLEED	0	0
11	SKIN RASH	0	0
12	COUGH	14	28
13	JOINT PAINS	1	2
14	DYSURIA	2	4



All the cases presented with fever of which 12% also had associated chills. Vomiting was a complaint in 46% ,diarrhoea was seen in 24% and pain abdomen was present in 28%.Cough was also seen in 28%.Few cases also reported nausea (4%),headache (10%),loss of appetite (6%),joint pains (2%) and dysuria (4%).None of the cases had constipation,GI bleed or skin rashes.

CLINICAL SIGNS

SL. NO.	SIGNS	NO. OF CASES (n=50)	PERCENTAGE (%)
1	PYREXIA	50	100
2	TOXIC LOOK	8	16
3	COATED TONGUE	3	6
4	PALLOR	2	4
5	JAUNDICE	1	2
6	ROSE SPOTS	0	0
7	LYMPHADENOPATHY	0	0
8	HEPATOMEGALY	24	48
9	SPLENOMEGALY	13	26
10	JOINT SWELLING	1	2
11	CHEST SIGNS	0	0
12	CNS COMPLICATIONS	0	0
13	CVS COMPLICATIONS	0	0



All the cases had pyrexia though only 16% had a toxic look.Coated tongue was seen in 3 cases(6%),pallor in 2 cases (4%) and jaundice in 1 case (2%).Hepatomegaly was a feature in 24 cases or 48% and splenomegaly in 13 cases or 26%.1 case had joint swelling.None of the cases included had rose spots,lymphadenopathy, chest signs, CNS or CVS complications.

CLINICAL SYMPTOMS IN DIFFERENT AGE GROUPS

SL. NO.	SYMPTOMS	NO OF CASES (n=50)		
		0-5 YRS	**6-10YRS**	**11-15YRS**
1	**FEVER**	11	13	26
2	**CHILLS**	3	2	1
3	**NAUSEA**	1	1	0
4	**VOMITING**	6	12	5
5	**HEADACHE**	2	2	1
6	**LOSS OF APPETITE**	1	1	1
7	**DIARRHEA**	2	5	5
8	**CONSTIPATION**	0	0	0
9	**PAIN ABDOMEN**	1	6	4
10	**G.I. BLEED**	0	0	0
11	**SKIN RASH**	0	0	0
12	**COUGH**	3	4	7
13	**JOINT PAINS**	0	1	0
14	**DYSURIA**	0	2	0

Vomiting as a symptom was more common in the age group 6-10yrs old.Diarrhoea was less common in 0-5 yrs old compared to the other 2 age groups.Pain abdomen was a complaint mainly in the 6-10 yrs and 11-15 yrs age group.Cough was most common in 11-15 yrs old.Joint pain and dysuria were seen only in 6-10 yrs age group.

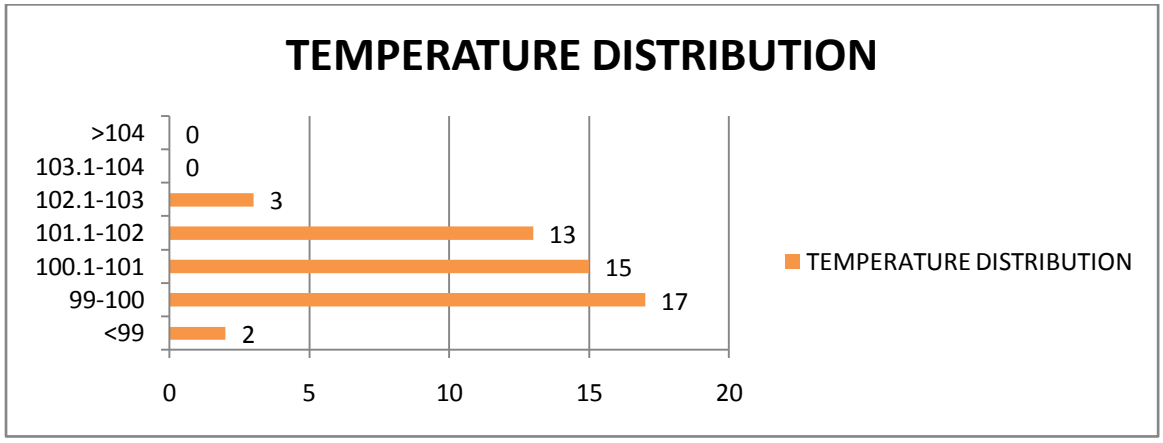
CLINICAL SIGNS IN DIFFERENT AGE GROUPS

SL. NO.	SIGNS	NO. OF CASES (n=50)		
		0-5YRS	6-10YRS	11-15YRS
1	PYREXIA	11	13	26
2	TOXIC LOOK	2	2	4
3	COATED TONGUE	1	2	0
4	PALLOR	0	2	0
5	JAUNDICE	0	1	0
6	ROSE SPOTS	0	0	0
7	LYMPHADENOPATHY	0	0	0
8	HEPATOMEGALY	9	8	7
9	SPLENOMEGALY	2	4	7
10	JOINT SWELLING	1	0	0
11	CHEST SIGNS	0	0	0
12	CNS COMPLICATIONS	0	0	0
13	CVS COMPLICATIONS	0	0	0

Splenomegaly was more common in 11-15 yrs age group.Pallor and jaundice were noted only in 6-10yrs age group.Joint swelling was found in only 1 case and was of 0-5 yrs age group.Most other signs had almost equal aedistribution.

TEMPERATURE PROFILE AT TIME OF ADMISSION

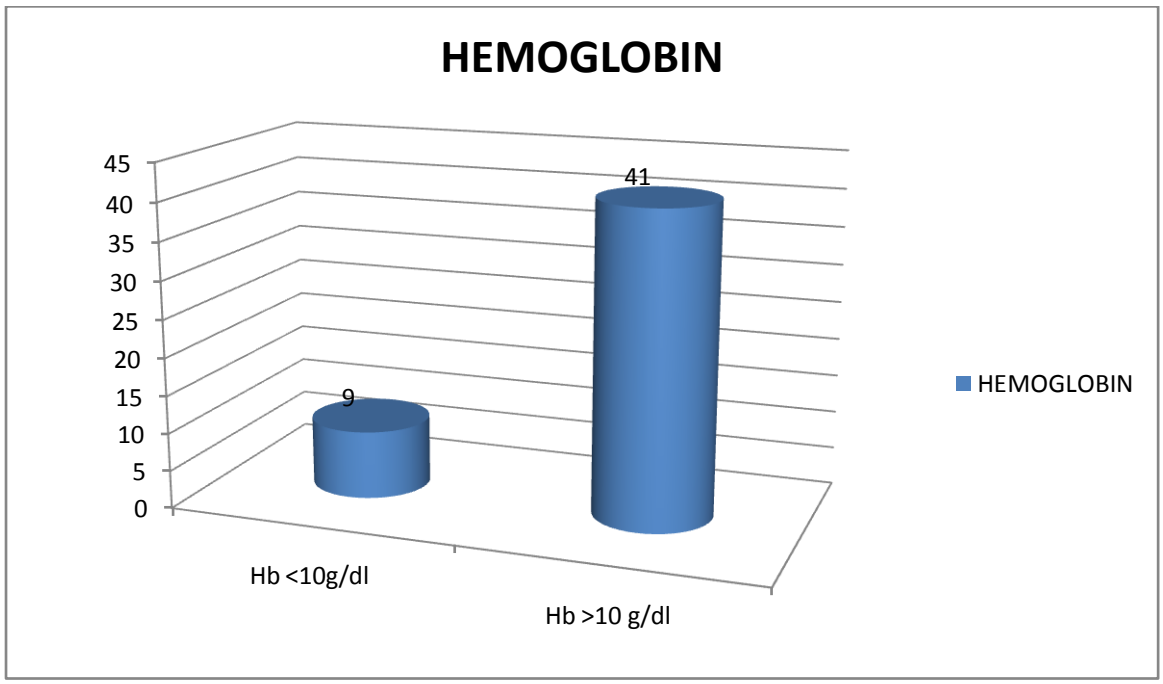
TEMPERATURE (°F)	NO. OF CASES (n=50)	PERCENTAGE (%)
<99	2	4
99 – 100	17	34
100.1 – 101	15	30
101.1 – 102	13	26
102.1 – 103	3	6
103.1 – 104	0	0
>104	0	0



4% of cases had no fever at admission.34%5 had temperature between 99-100 °F,30% had fever between 100.1-101 °F and 26% had fever between 101.1-102 °F.Therefore most of the cases had temperatures falling within 99-102°F.None of the cases had temperatures more than 103 °F.

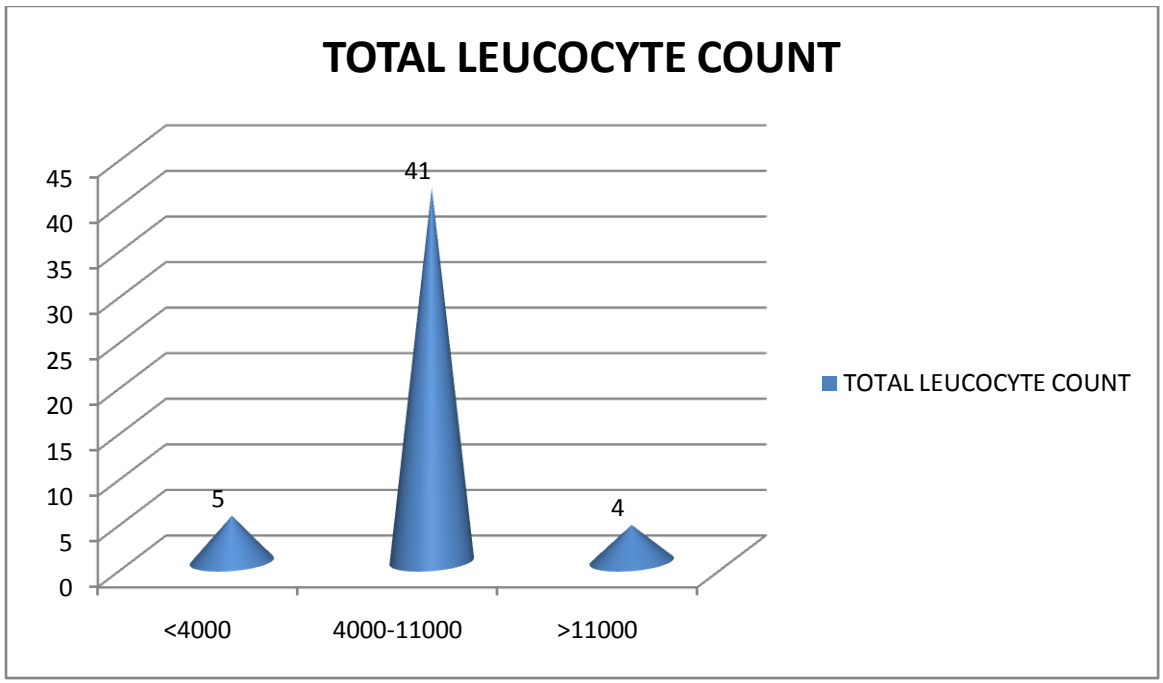
BLOOD PROFILE

HEMOGLOBIN	NO. OF PATIENTS (n=50)	PERCENTAGE (%)
• <=10g%	9	18
• >10g%	41	82



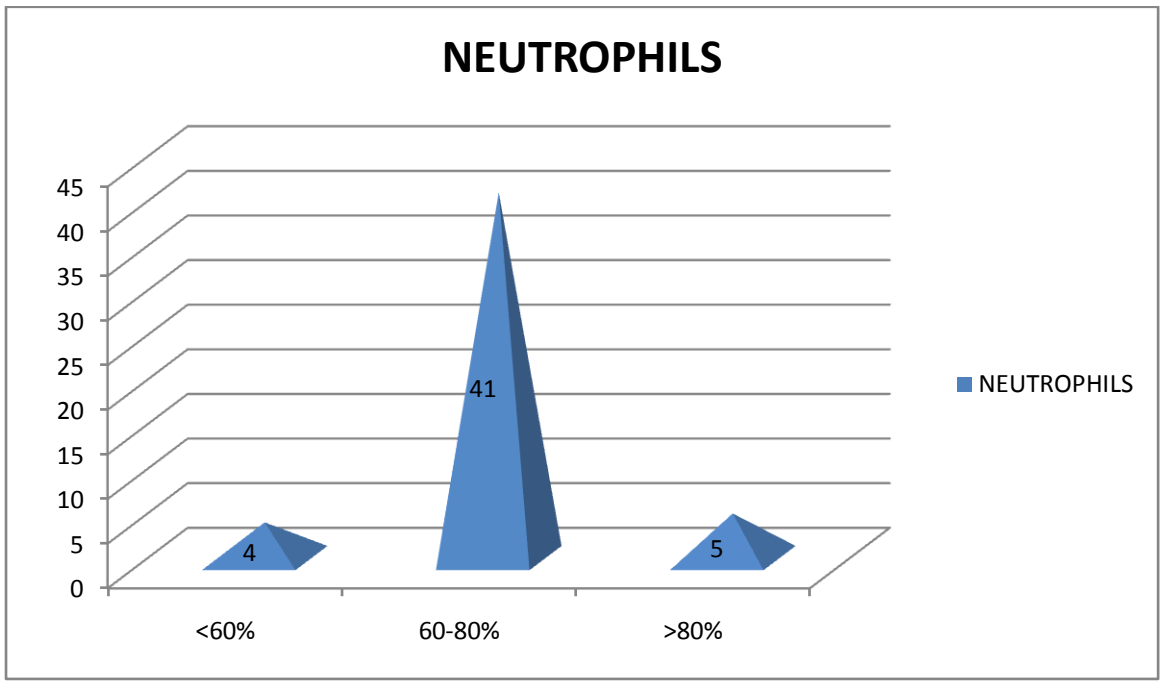
In our study, majority of 42 cases (82%) did not have anemia as a feature. Only 9 cases (18%) had haemoglobin less than 10mg/dl.

TOTAL LEUCOCYTE COUNT	NO. OF PATIENTS (n=50)	PERCENTAGE (%)
• **<4000/cumm**	5	10
• **4000-10000/cumm**	41	82
• **>10000/cumm**	4	8



41 cases or 82% had normal leucocyte counts between 4000-11000 cells/cumm.Only 5 cases or 10% had leucopenia with cells <4000/cumm and only 4 cases or 8% had leucocytosis with cells >11000/cumm.

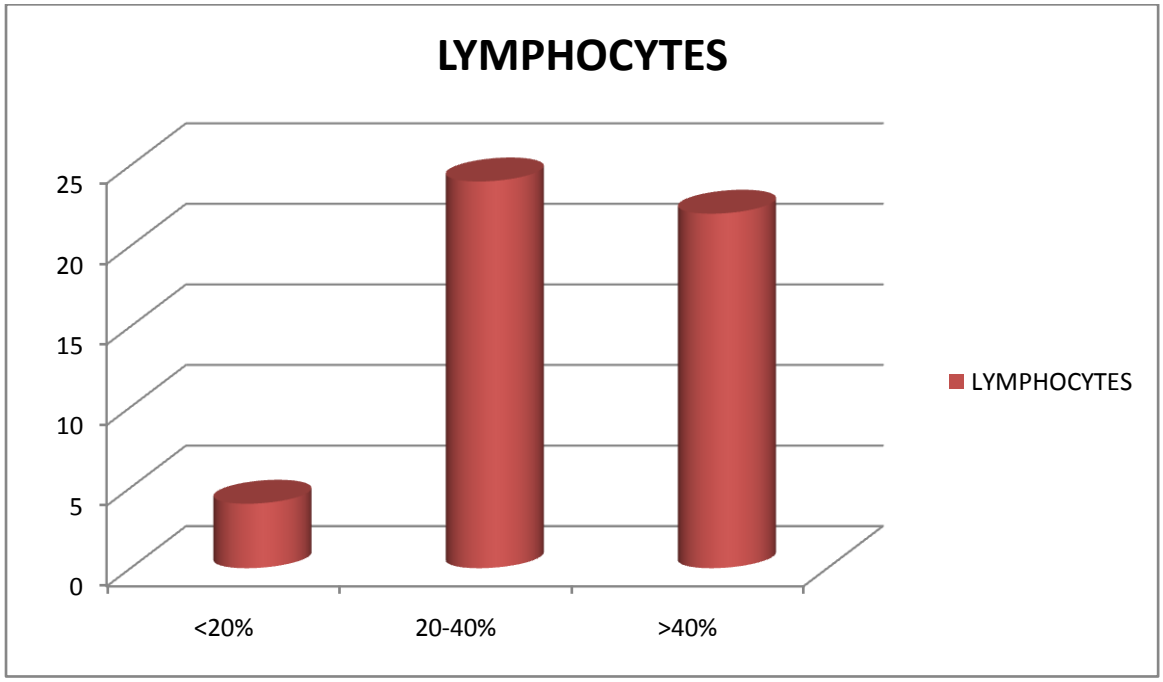
NEUTROPHILS	NO. OF CASES(n=50)	PERCENTAGE (%)
<60%	4	8
60-80%	41	82
>80%	5	10



In our study,41 cases or 82% had normal neutrophil count of 60-80% whereas 4 cases or 8% had neutropenia with neutrophils <60% and 5 cases or 10% had neutrophilia with neutrophils >80%.

LYMPHOCYTES

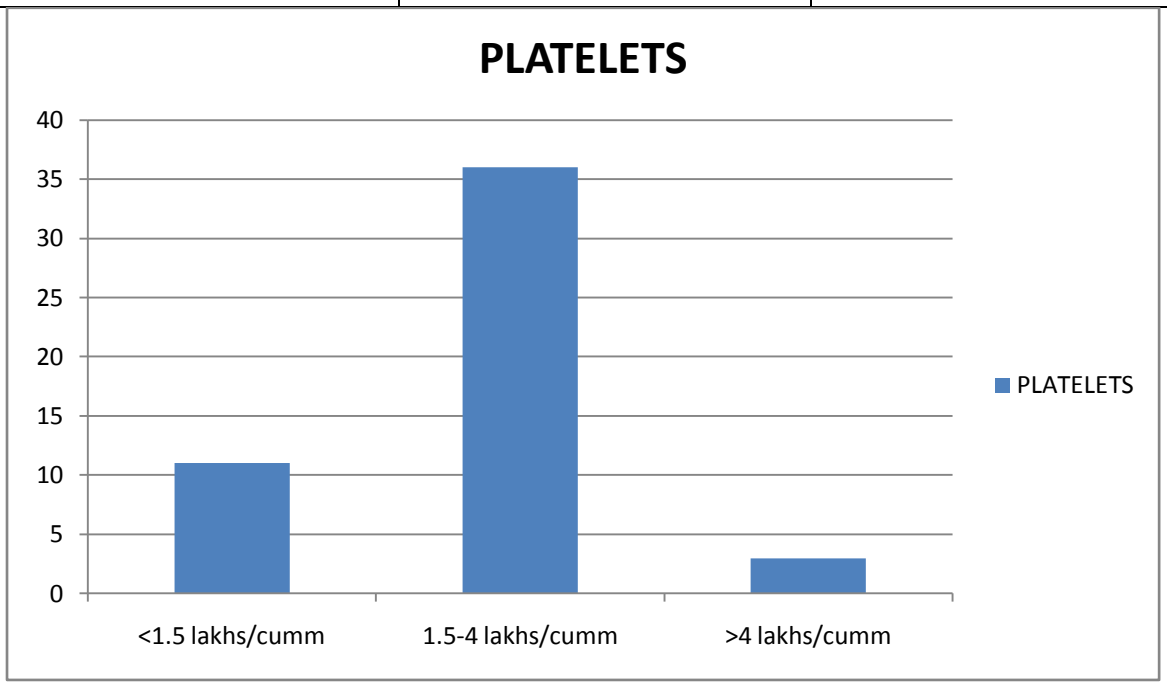
LYMPHOCYTES	NO. OF CASES(n=50)	PERCENTAGE (%)
<20%	4	8
20-40%	24	48
>40%	22	44



In our study 24 cases or 48% had normal lymphocyte counts between 20-40% and 22 cases or 44% had lymphocytosis with lymphocyted >40%.4 cases or 8% had lymphopenia with <20% lymphocytes.

PLATELET COUNT

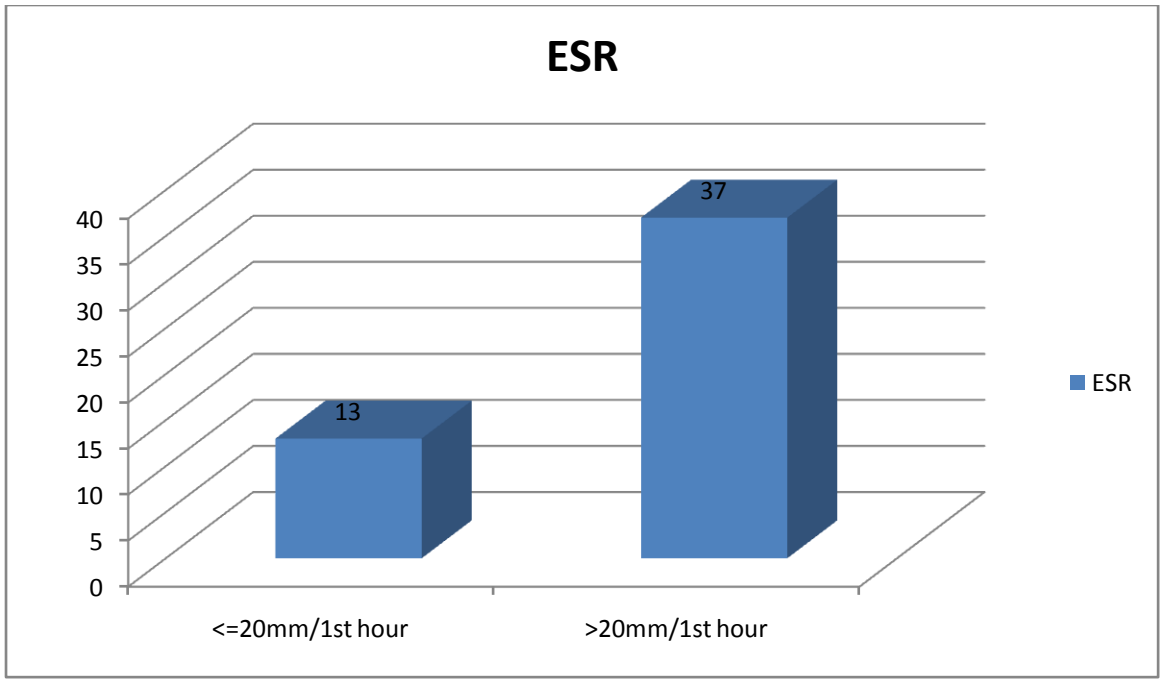
PLATELETS	NO. OF CASES(n=50)	PERCENTAGE
<1.5 lakhs/cumm	11	22
1.5-4 lakhs/cumm	36	72
>4 lakhs/cumm	3	6



36 cases or 72% had normal platelet counts between 1.5-4 lakhs/cumm and 11 cases or 22% had thrombocytopenia with counts less than 1.5lakhs/cumm.3 cases or 6% had thrombocytosis with counts more than 4 lakhs/cumm.

ESR

ESR	NO. OF PATIENTS(n=50)	PERCENTAGE (%)
<=20 MM/1ST HOUR	13	26
>20 MM/1ST HOUR	37	74



37 cases or 74% had raised ESR (>20mm/1st hour) at presentation and only 13 or 26% had normal ESR in our study.

COMPARISON OF WIDAL WITH BLOOD CULTURE (n=86)

		BLOOD CULTURE		TOTAL
		POSITIVE	**NEGATIVE**	
WIDAL	**POSITIVE**	**21**	**6**	**27**
	NEGATIVE	**29**	**30**	**59**
TOTAL		**50**	**36**	**86**

In the above 2 X 2 contingency table, the Chi-square 6.236 for the association between the Widal test and the Blood culture test is significant ($P< 0.01$). It can be inferred that there is a significant difference in the two tests. Out of the 50 blood cultured positive cases which was considered as the gold standard, was compared with the Widal test and only 21 cases showed positive and 29 negative results. 6 cases out of 36 negative cases in blood test showed positive in Widal test. The Widal test has a Sensitivity of 77%: specificity of 51 % ; Positive predictive value of 58% and Negative predictive value of 16% when compared with blood culture result.

WIDAL REACTION IN BLOOD CULTURE POSITIVE PATIENTS

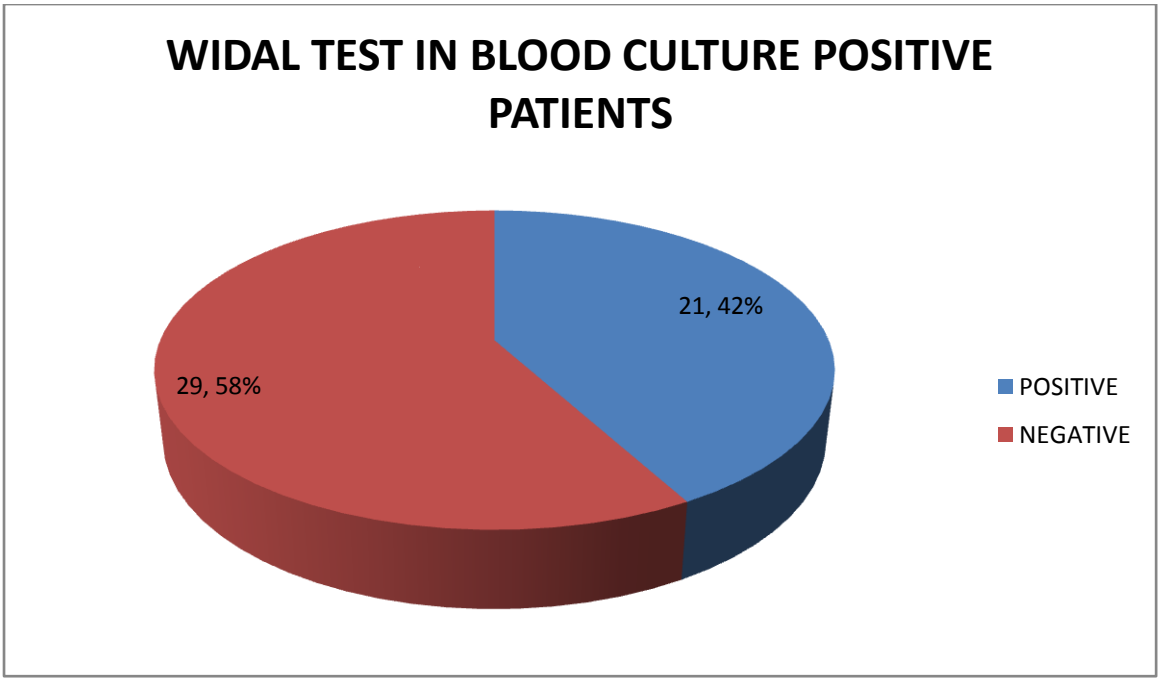
WIDAL REACTION in Blood culture positive patients	NO. OF CASES (n=50)	PERCENTAGE (%)
POSITIVE	21	42
NEGATIVE	29	58
TOTAL	50	100%

WIDAL TITRE T O

WIDAL TITRE	FREQUENCY	PERCENTAGE (%)
<=1:80	32	64
1:160	6	12
1:320	7	14
>= 1:640	5	10
TOTAL	50	100

WIDAL TITRE T H

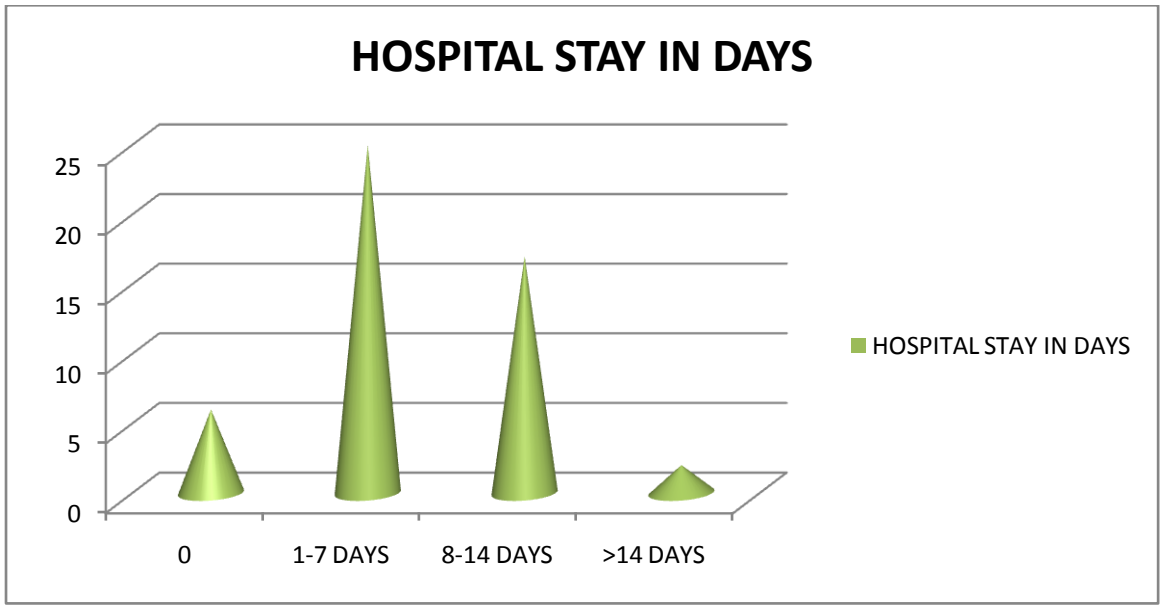
WIDAL TITRE	FREQUENCY (n=50)	PERCENTAGE (%)
<=1:80	33	66
1:160	6	12
1:320	7	14
>=1:640	4	8
TOTAL	50	100



The Widal test was done at presentation.Of the 50 blood culture positive cases,Widal test was positive in 21 cases (42%), and negative in 29 cases (58%). Titres more than or equal to 1:160 were taken as positive.O agglutin was positive in the ratio 1:160 in 12%, 1:320 in 14% and ≥1:640 in 10%.H agglutinin was positive in the ratio 1:160 in 12%,1:320 in 14% and ≥1:640 in 8%.

DURATION OF HOSPITAL STAY

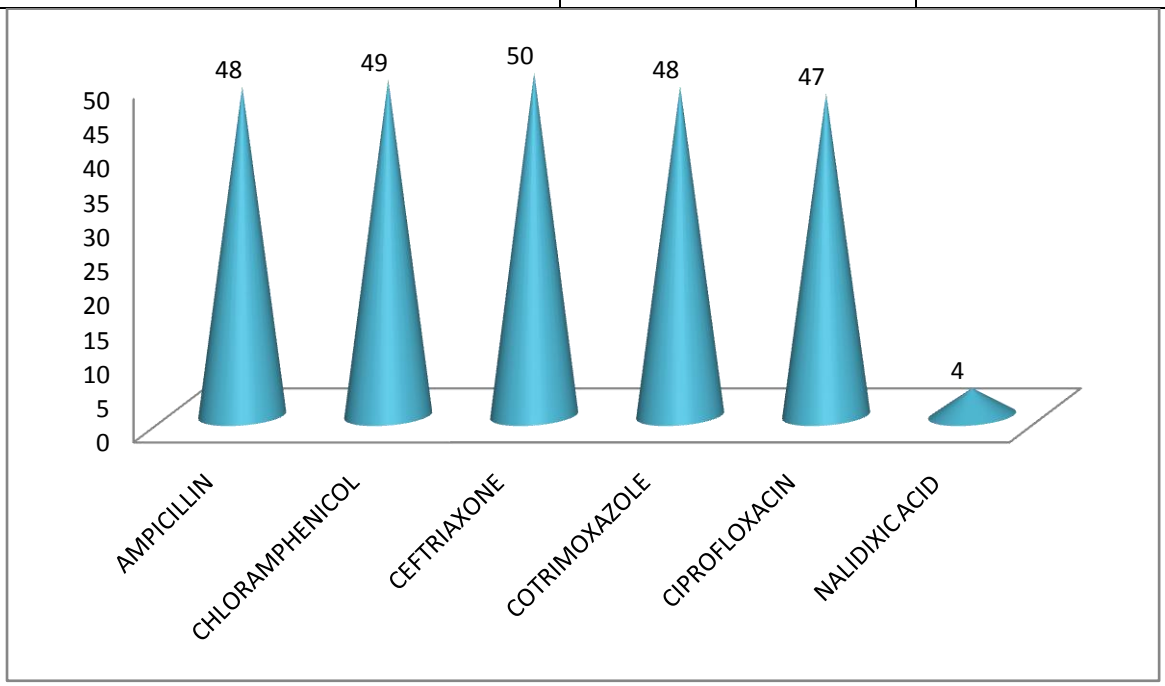
DURATION OF HOSPITAL STAY IN DAYS	NO. OF CASES (n=50)	PERCENTAGE (%)
0	6	12
1-7	25	50
8-14	17	34
>14	2	4



6 cases or 12% did not require admission,25 cases or 50% were admitted for less than or equal to a week,17 cases or 34% were admitted for 8-14 day and only 2 cases or 4% required admission more than 2 weeks.Of the 50 cases,only 7 required intensive unit care.

DRUG SENSITIVITY PATTERN

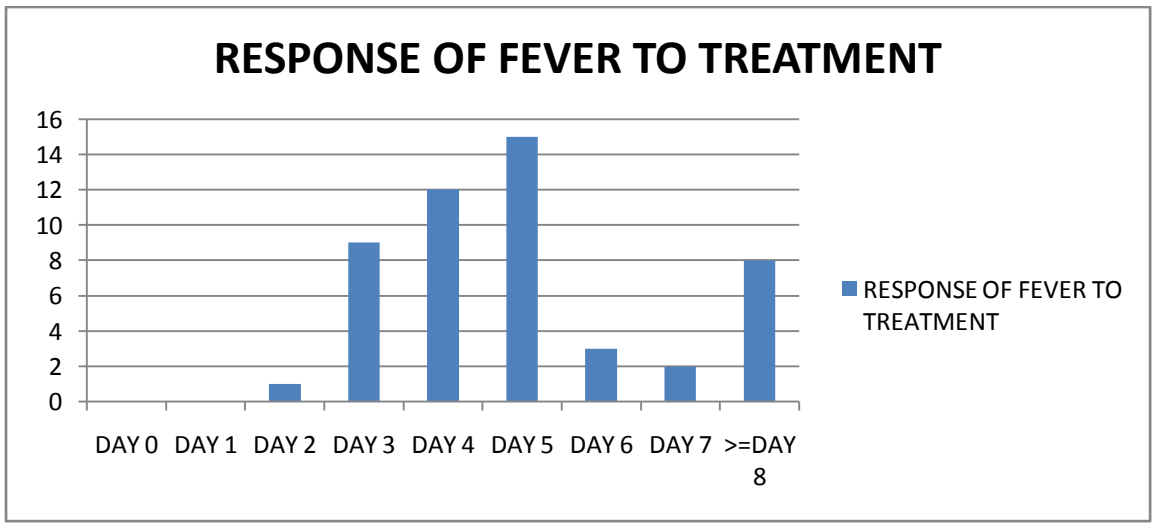
ANTIBIOTIC (n=50)	NO. OF CASES SENSITIVE	PERCENTAGE (%)
• AMPICILLIN	48	96
• CHLORAMPHENICOL	49	98
• CEFTRIAXONE	50	100
• COTRIMOXAZOLE	48	96
• CIPROFLOXACIN	47	94
• NALIDIXIC ACID	4	8



In our study,all the cases were responsive to Ceftriaxone,most were responsive to Ampicillin (48 cases,96%), Chloramphenicol (49 cases,98%),Cotrimoxazole (48 cases,96%) and Ciprofloxacin (47 cases,94%).Out of 50,only 4 cases responded to Nalidixic acid ie only 8% were sensitive.Therefore a total of 46 cases were resistant to Nalidixic acid ie 92% were resistant to it.

RESPONSE OF FEVER TO ANTIBIOTIC THERAPY

DAY OF SUBSIDENCE OF FEVER FOLLOWING INITIATION OF ANTIBIOTIC THERAPY	NO. OF CASES (n=50)	PERCENTAGE (%)
Day 0	0	0
Day 1	0	0
Day 2	1	2
Day 3	9	18
Day 4	12	24
Day 5	15	30
Day 6	3	6
Day 7	2	4
>=Day 8	8	16
TOTAL	50	100



Following initiation of antibiotic therapy,majority (72%) had subsidence of fever from day 3 to day 5.None of the cases had defervescence before initiation

of antibiotics or on day 1 of initiation.8 cases or 16% responded only after more than a week of antibiotic therapy.

The mean period of defervescence was 4.96 days.A minimum of 2 days and maximum of 8 days is noted.A standard deviation of 1.689 is seen.

Of the 50 cases,Ceftriaxone was the antibiotic given to 38 patients and the other 12 received Ciprofloxacin.

RESPONSE TO CEFTRIAXONE

DAY OF SUBSIDENCE OF FEVER FOLLOWING INITIATION OF CEFTRIAXONE	NO. OF CASES (n=38)	PERCENTAGE (%)
Day 0	0	0
Day 1	0	0
Day 2	1	2.63
Day 3	7	18.42
Day 4	9	23.68
Day 5	12	31.57
Day 6	2	5.26
Day 7	1	2.63
>=Day 8	6	15.78
TOTAL	38	100

In the patients who received Ceftriaxone,there was defervescence of fever mainly between days 3 to 5 and amounted to 73.67%.15.78 % of cases took atleast a week to respond.

RESPONSE TO CIPROFLOXACIN

DAY OF SUBSIDENCE OF FEVER FOLLOWING INITIATION OF CIPROFLOXACIN	NO. OF CASES (n=12)	PERCENTAGE (%)
Day 0	0	0
Day 1	0	0
Day 2	0	0
Day 3	2	16.66
Day 4	3	25
Day 5	3	25
Day 6	1	8.33
Day 7	1	8.33
>=Day 8	2	16.66
TOTAL	12	100

Of the patients who were on Ciprofloxacin,66.66% responded by days 3-5.16.66% of patients took atleast a week to respond.

DISCUSSION

This study was conducted as a retrospective observational study among the inpatients and outpatients of the department of Paediatrics of PSG IMSR with confirmed diagnosis of Salmonella typhi including locales in and around Coimbatore and also including referred cases.The study spanned over a period of 18 months from June 2011 to November 2012.

Of the 50 cases included in the study,26 cases (52%) fell in the age group of 11-15 years.26% ie 13 cases were of the 6-10 years age group and 22% or 11 cases were of the 0-5 years age group.There was only a single infant case.Walia et al[56] reported that 21.7% were children aged under 5 years and 6.1% were under 2 years.Yaramis et al[54] reported that 17% of patients were children under 5 years and that school children were most affected.

Sinha A et al[4] and Leon Ochiai et al[2] reported that the incidence in preschool children and school going children were similar.

In our study, 36 out of the 50 cases were males and amounted to 72% and only 14 cases were females and amounted to only 28% .Males were predominant in the studies by Yaramis et al[54],Garg K et al[19] and Raghuram et al[38].

Out of the 50 cases included in the study, majority of the cases were of the age group 11-15 years and of them 19 were male and only 7 were female.In all 3 selected age groups,males were the majority.

34 of the 50 cases ie 68% had fever of 1-7 days prior to admission.Only 10% had fever of more than 2 weeks duration.

Comparison of presenting symptoms in various studies in percentage

SYMPTOMS	**K.Garg et al[19]**	**R.K.Arora et al[26]**	**Sharma, Gathwala[39]**	**Bhutta[20]**	**Present study**
FEVER	100	100	100	95	100
CHILLS	39	42.7	45	-	12
VOMITING	41	30	29	39	46
HEADACHE	-	28.1	-	12	10
PAIN ABDOMEN	28	-	-	28	22
DIARRHOEA	-	14.5	9.2	35	24
CONSTIPATION	-	-	1.5	11	-
GI BLEED	-	-	-	-	-
BURNING MICTURITION	-	-	-	-	4
COUGH	36	37.8	29.2	-	28

All the cases presented with fever which is consistent with the findings of K.Garg et al,R.K Arora et al and Sharma,Gathwala.Bhutta [22] reported fever in 95% of cases only.

In our study 12% also had associated chills which is much lesser than that reported by K.Garg, R.K Arora and Sharma.

Vomiting was a complaint in 46% and is consistent with K.Garg's and Bhutta's[22] study though it is much higher than studies by RK Arora and Sharma.Diarrhoea was seen in 24% and has a higher incidence in our study compared to all except Bhutta.Pain abdomen was present in 28% which is consistent with the findings of K.Garg and Bhutta.Cough was also seen in 28% which is similar to Sharma's findings but lesser than that of K.Garg and R.K Arora.Few cases also reported nausea,headache,loss of appetite,joint pains and dysuria.None of the cases had constipation,GI bleed or skin rashes which is similar to K.Garg[19],RK Arora[26] and Sharma[39].Bhutta[20] reported constipation in 11%.

Vomiting as a symptom was more common in the age group 6-10yrs old.Diarrhoea was less common in 0-5 yrs old compared to the other 2 age groups.Pain abdomen was a complaint mainly in the 6-10 yrs and 11-15 yrs age group.Cough was most common in 11-15 yrs old.Joint pain and dysuria were seen only in 6-10 yrs age group.

COMPARISON OF SIGNS WITH SIMILAR STUDIES IN PERCENTAGE

SIGNS	**K.Garg et al**[19]	**R.K.Arora et al**[26]	**Raghuraman et al**[38]	**Bhutta** [20]	**Present study**
PYREXIA	100	100	100	95	100
TOXIC LOOK	28	39.8	30	33	16
COATED TONGUE	-	33	-	-	6
PALLOR	10	57.2	-	-	4
JAUNDICE	1.4	1	6	2	2
ROSE SPOTS	-	-	-		-
SPLENOMEGALY	55	90	45	20	26
HEPATOMEGALY	60	45.6	88	41	48
LYMPHADENOPATHY	-	-	-	-	-
CHEST SIGNS	-	8.7	-	-	-
CNS COMPLICATIONS	-	-	-	-	-
CVS COMPLICATIONS	-	-	-	-	-

All the cases had pyrexia in our study which is consistent with the other 3 studies except Bhutta who reported pyrexia in 95% of cases.Only 16% had a toxic look which is lesser than that in studies of K.Garg, RK Arora,

Raghuraman and Bhutta.Coated tongue was seen in 6 percent,pallor in 4% and jaundice in 2%.Hepatomegaly was a feature in 48% which is similar to RK Arora and Bhutta and lesser than that of K.Garg and Raghuraman.In our study splenomegaly was noted in 26% which is lesser than the other three studies except Bhutta who reported it in 20%.1 case had joint swelling.None of the cases included had rose spots,lymphadenopathy, chest signs, CNS or CVS complications which is similar to the other 4 studies.

Splenomegaly was more common in 11-15 yrs age group.Pallor and jaundice were noted only in 6-10yrs age group.Joint swelling was found in only 1 case and was of 0-5 yrs age group.Most other signs had almost equal distribution.

Sinha A et al reported that typhoid may present in a more dramatic form in children less than 5 years old with higher rates of complications and hospitalizations.[4]

45 of the cases (90%) had temperatures falling within 99-102 °F.None of the cases had temperatures more than 103 °F.

In our study,majority (82%) did not have anemia as a feature. Only 9 cases (18%) had haemoglobin less than 10mg/dl. Yaramis et al[54] reported anemia in 38% of cases.In cases of severe fall in haemoglobin levels,one should rule out gastrointestinal bleed or hemolysis or an alternative diagnosis.

82% of the cases had normal leucocyte counts and only 10% had leucopenia and only 8% had leucocytosis. Sinha A[4] and Bhutta ZA[20,22] reported blood leucocye counts to be low in relation to fever and toxicity but the range is wide and they also reported leucocytosis upto 25,000cells/cumm in younger children.RA Garg reported leucopenia in 16.7% and RK Arora reported it in 10.7%.

In our study,82% had normal neutrophil count whereas 8% had neutropenia and 10% had neutrophilia.

44% had lymphocytosis and 48% had normal lymphocyte counts.

72% had normal platelet counts,22% had thrombocytopenia and 6% had thrombocytosis.Yaramis reported thrombocytopenia in 10%.

75% had raised ESR at presentation and only 26% had normal ESR in our study.

Widal test was compared with blood culture in the 86 initially chosen casesheets and the Chi-square 6.236 for the association between the Widal test and the Blood culture test is significant ($P< 0.01$). Thus it can be inferred that there is a significant difference in the two tests. The 50 blood cultured positive cases, which was considered as the gold standard, was compared with the Widal test and only 21 cases showed positive and 29 negative results. 6 cases out of 36 negative cases in blood test showed positive in Widal test. The Widal test

has a Sensitivity of 77%: specificity of 51 % ; Positive predictive value of 58% and Negative predictive value of 16% when compared with blood culture result.Yaramis et al [54] reported that of the 67 patients with blood culture positive for S.typhi in their study,23 also had positive Widal serology. Olsen et al[60] and Parry[61] et al reported that though the Widal test is commonly used for the diagnosis of typhoid fever,it is unreliable especially in endemic areas.

Of the 50 blood culture positive cases,Widal test was positive in 21 cases (42%), and negative in 29 cases (58%). Titres more than or equal to 1:160 were taken as positive.O agglutin was positive in the ratio 1:160 in 12%, 1:320 in 14% and ≥1:640 in 10%.H agglutinin was positive in the ratio 1:160 in 12%,1:320 in 14% and ≥1:640 in 8%.

Parry et al[61] reported that O-agglutinin titer was ≥100 in 83% of the blood cuture positive typhoid fever cases and H-agglutinin titer was ≥ 100 in 67%.[71] Yaramis et al reported that of the 23 patients with positive Widal and blood culture,agglutination titers of at least 160 were positive in all children.[54]

In our study,all the cases were responsive to Ceftriaxone (100% sensitive).Chowta et al[64] and Jog et al[66] also had similar results. Most were responsive to Ampicillin (48 cases,96%), Chloramphenicol (49 cases,98%),Cotrimoxazole (48 cases,96%) and Ciprofloxacin (47 cases,94%).Out of 50,only 4 cases responded to Nalidixic acid.Thus there was 92% resistance for Nalidixic acid in our study.Significant resistance to Nalidixic

acid was also noted in studies by Jog S et al[66] and Walia M et al [67]. Walia et al reported that Nalidix acid resistance is a marker for the prediction of low level resistance of ciprofloxacin among Salmonella typhi and also an indicator of treatment failure to ciprofloxacin.The CLSI now recommends tha all S.typhi isolates are to be screened for nalidixic acid resistance along with ciprofloxacin[62].Nagshetty et al[63] reported that Nalidixic acid resistance was reported in 31.5% and was associated with an increase in Ciprofloxacin MIC.

Majority of cases responded to antibiotic therapy within days 3 to 5 of initiation.16% responded only after more than a week of antibiotics. The mean period of defervescence was 4.96 days.A minimum of 2 days and maximum of 8 days is noted.A standard deviation of 1.689 is seen.

Of the 50 cases,Ceftriaxone was the antibiotic given to 38 patients and the other 12 received Ciprofloxacin.

Kumar R,Gupta N and Shalini conducted a study to evaluate multi drug resistant typhoid fever and therapeutic response of ofloxacin and ceftriaxone and reported that hose children treated with ceftriaxone had a shorter time to defervescence compared to ofloxacin with a mean of 4.258 and 4.968 respectively.[24]

12% did not require admission for treatment.50% were admitted for less than or equal to a week.34% for 8-14 days and 4% for more than 2 weeks.

CONCLUSION

50 cases were included in our study.Of them 52% were of the age group 11-15 years.

Males were predominant in all 3 age groups.

All the cases included presented with fever,majority of whom had fever of less than or equal to a week at presentation.

Other common symptoms were chills,headache,vomiting, diarrhoea and cough.

Pyrexia was noted in all patients and other common signs were toxic look,hepatomegaly and splenomegaly.

Majority had normal leucocyte counts with relative lymphocytosis.

Widal test is a simple,fast,cheap and easily available test though its reliability is not recommendable as not all patients with blood culture positive for Salmonella showed a positive Widal.However there is a significant association between blood culture and Widal test.

Majority of the cases were resistant to Nalidixic acid and is thus not recommended at present.Nalidixic acid resistance also implies that a higher dose of Ciprofloxacin is required.All the cases were sensitive to Ceftriaxone.Most were responsive to Ampicillin,Chloramphenicol,Cotrimoxazole and Ciprofloxacin.

Majority of cases responded to antibiotic therapy within days 3 to 5 of initiation.

BIBLIOGRAPHY

1. World Health Organization.The diagnosis,treatment and prevention of typhoid fever.Communicable disease surveillance and response vaccines and biologicals.Geneva WHO 2003;1-18
2. Ochiai RL, Acosta CJ, Danovaro-Holliday MC, Baiqing 2. D, Bhattacharya SK, Agtini MD, *et al*; Domi typhoid study group. A study of typhoid fever in five Asian countries: disease burden and implications for controls. Bull World Health Organ2008; 86 : 260-8.
3. Punjabi NH.Cost evaluation of typhoid fever in Indonesia.Medical Journal of Indonesia 1998;7(S):90-93
4. Sinha A,Sazawal S,Kumar R,Sood S,Reddaiah VP,Singh B et al.Typhoid fever in children less than 5 years.The Lancet 1999;354:734-6
5. Saha MR,Dutta P et al.A note on incidence of typhoid fever in diverse age groups in Kolkata,India.Jpn J Infect Dis 200;56:121-2
6. Levine MM,Black R,Lanata C,Chilean Typhoid Committee.Precise estimation of the number of chronic carriers of Salmonella typhi in Santiago,Chile,an endemic area.The Journal of Infectious Diseases 1982;146(6):724-6
7. Crump JA, Kretsinger K, Gay K, et al. Clinical response and outcome of infection with Salmonella enterica serotype Typhi with decreased susceptibility to fluoroquinolones: a United States FoodNet multicenter

retrospective cohort study. Antimicrob Agents Chemother 2008; 52: 1278–84.

8. Lynch MF, Blanton EM, Bulens S, et al. Typhoid fever in the United States, 1999–2006. JAMA 2009; 302:859–65.
9. Kundu R,Ganguly N et al.IAP Task Force report:diagnosis of Enteric fever in children.Indian Pediatrics 2006;43:875-933
10. Wain J,Diep TS et al.Quantitation of bacteria in blood of typhoid fever patients and relationship between counts and clinical features,transmissibility and antibiotic resistance.Journal of Clinical Microbiology 1998;36:1683-7
11. Wain J,Bay PVB et al.Quantitation of bacteria in bone marrow from patients with typhoid fever.Relationship between counts and clinical features.J Clin Microbiol 2001;39(4):1571-5
12. Kaul PA,Waheed A,Shah PA et al.Widal reaction.Jour Assoc Phy India 1993;41:617-618
13. Pang T,Puthucheary S.Significance and value of Widal test n the diagnosis of typhoid fever in an endemic area.J.Clin Patho 1986;36:471-475
14. Bhutta ZA,Mansurali N.Rapid serologic diagnosis of pediatric typhoid fever in an endemic area: a prospective comparative evaluation of two dot-enzyme immunoassays and the Widal test.The American Journal of Tropical Medicine and Hygiene 1999;61(4):654-7

15. Lim PL,Tam FCH,Cheong YM,Yegathesan M.One step 2 minute test to detect typhoid specific antibodies based on particle separation in tubes.Journal of Clinical Microbiology 1998;36(8):2271-8
16. Choo KE,Oppenheimer SJ,Ismail AB,Ong KH.Rapid serodiagnosis of typhoid fever by dot enzyme immunoassay in an endemic area.Clinical Infectious Diseas.1994;19:172-176
17. Dutta S,Sur D,Manna B,Sen B et al.Evaluation of new generation serologic tests for the diagnosis of typhoid fever: data from a community based surveillance in Calcutta,India.Diagn Microbiol Infect Dis 2008;56(4):359-65
18. Rasaily R,Dutta P,Saha MR,Mitra U et al.Multidrug resistant typhoid fever in hospitalized children:clinical,bacteriological and epidemiological profiles.Eur J Epidemio 1994:10:41-46
19. K.Garg et al.Clinical profile of multidrug resistant typhoid fever from Jaipur city.Indian Pediatrics.1994;31:191-192
20. Bhutta ZA,Naqvi SH et al.Multidrug resistant typhoid in children.Presentation and Clinical features.Rev Infect Dis 1991;13:832-836
21. Kaul PB,Murli MV,Sharma PP et al.Multidrug resistant Salmonella typhi infection – Clinical profile and therapy.Indian Pediatric Journal 1991;28:357-361
22. Bhutta ZA. Impact of age and drug resistance on mortality in typhoid fever. Arch Dis Child 1996;75:214-7.

23. Rowe B, Ward LR, Threlfall EJ. Multidrug-resistant Salmonella typhi: a worldwide epidemic. Clin Infect Dis 1997;24(1):106-9.

24. Kumar R,Gupta N,Shalini.Multidrug resistant typhoid fever.Ind J Paediatr 2007;74:39-42

25. Rowe B,Ward LR, Threlfall EJ.Ciprofloxacin resistant salmonella typhi in the UK.Lancet 1995;345:1302

26. R.K. Arora et al.Multidrug resistant typhoid fever study of an outbreak in Calcutta.Indian Pediatrics, 1992;29:62-63

27. Christie AB.Typhoid and paratyphoid fevers.Infectious diseases,Epidemiology and clinical practice.4th edition,100-163

28. Ananthanarayanan R,Panikar CKJ. Textbook of Microbiology.Chennai:Orient Longman 8th edition 2004;288

29. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever.Bull World Health Organ 2004; 82:346–53.

30. Chart H,Cheasty T et al.Serodiagnosis of Salmonella enteric serovar Typhi and S.enterica serovars Paratyphi A,B and C human infections.Journal of Medical Microbiology 2007;56:1161-1166

31. Bhutta ZA.Nelson Textbook of Pediatrics,Elsevier 19th edition 2011,954-9

32..Amdekar YK.IAP Textbook of Pediatrics.4th edition,2009:384-8

33. Parks Textbook of Preventive and Social Medicine.21st edition,2011;212-5

34. Washington Winn C,Kissan John M.Bacterial diseases.Andersons Textbook of Pathology.Mosby 10th edition,1996:785-789

35. Samuelson John.Salmonellosis and typhoid fever.Robbins Pathologic Basis of DiseaseElsevier .6th edition,2011:356-357

36. Udani PM,Dasteur DK.Typhoid fever.Textbook of Pediatrics 960-972

37. Richen J. Typhoid and paratyphoid fevers.Oxford textbook of Medicine. Oxford University Press 5th edition 560-562

38. T.S.Raghuraman et al.Clinical profile and therapy in enteric fever.Indian Pediatrics.1994;31:197-198

39. Sharma,Gathwala.Clinical profile and outcome in enteric fever.Indian Pediatrics 1993;30:48-49

40. R.A.Garg et al.Typhoid fever before 2 years of age.Indian Pediatrics,1993;30:806-807

41. Tomraci SN,Singh S.Hepatobiliary complications of Typhoid fever.Indian Journal of Pediatrics 1993;30:720-724

42. Joshi et al.Complications, Prognosis, Relapse in Enteric fever.JIMA 1963;67-73

43. Giri Omprakash.Study of CSF in Typhoid Meningitis.Jour Assoc Phy India 1993;41-154

44. Bhutta ZA.Current concepts in the diagnosis and treatment of typhoid fever. *BMJ* 2006;333:78-82

45. Shivananda PG et al.Rapid diagnosis of Salmonella.Indian Ped 1984;21:463-467
46. Rajagopal V et al.Bone marrow culture in diagnosis of enteric fever.Indian Jour Path and Microb 1986;15-19
47. Fadeel MA,Crump JA,Mahoney FJ,Nakla IA et al.Rapid diagnosis of typhoid fever by enzyme linked immunosorbet assay detection of Salmonella serotype typhi antigens in urine.Am J Trop Med Hyg 2004;70(3):323-8
48. Gilman Rh,Terminel M et al.Relative efficacy of blood,urine,rectal swab,bone marrow and rose spot cultures for recovery of Salmonella typhi in typhoid fever.The Lancet 1975;1211-4
49. Karami A,Rajbar R et al.Rapid detection of different serovares of Salmonella enteric by multiplex PCR.Iranian J Publ Health 2007;36(2):38-42
50. Gotuzzo E,Carrillo C.Quinolones in typhoid fever.Infect Dis Clin Pract 1994;3:345-51
51. Ranju C,Pais P,Ravindran GD,Singh G.Changing pattern of antibiotic sensitivity of salmonella typhi.Natl Med J Ind 1998;11;266-7
52. Paediatrics Today:May-June 2005 VIII(3)
53. Chowta MN,Chowta NK.Study of clinical profile and antibiotic response in typhoid fever.Indian Journal of Medical Microbiology.2005;23(2):125-127
54. Yaramis ,Yildirim I,Katar S et al.Clinical and Laboratory presentation of typhoid fever.International Pediatrics.2001;16-4:227-231

55. Jog S,Soman R, Singhal T et al.Enteric fever in Mumbai-Clinical profile,sensitivity patterns and response to antimicrobials.Journal of the Association of Physicians of India.2008;56:237-240
56. Walia M,Gaind R et al.Current perspectives of enteric fever:a hospital based study from India. Ann Trop Paediatr. 2005 Sep;25(3):161-74.
57. Frenck RW Jr.,Mansour A,Nakhla I et al.Short course Azithromycin for the treatment of uncomplicated typhoid fever in children and adolescents.Clin Infect Dis 2004:38(7):951-7
58. Butler T,Sridhar CB,Daga MK et al.Treatment of typhoid fever with azithromycin versus chloramphenicol in a randomized multicentre trial in India.Journal of Antimicrobial Chemotherapy 1999;44:243-250
59. Mandell GL,Bernnett JE,Dolin R.Principles and practice of infectious diseases.6th edition,volume 2.Philadelphia:Elsevier Churchill Livingstone,2005:2636-50
60. Olsen Sj,Pruckler J,Bibb W,Nyugen TMT et al.Evaluation of rapid diagnostic tests for typhoid fever.J.Clin icrobiol.2004;42:1885-1889
61. Parry CM,Hien TT,Dougan G,White NJ,Farrar JJ.Typhoid fever.N. Engl. J. Med.2002;347:1770-1782

62. Wayne PA.Clinical and Laboratory Standards Institute (2006) Clinical and Laboratory Standards Institution:Methods for Dilution Antimicrobial Susceptibilty Tests for bacteria that grow aerobically.Approved standards,CLSI document M7-A7.

63. Nagshetty K,Channappa ST,Gaddad SM. Antimicrobial susceptibility of Salmonella typhi in India.*J Infect Dev Ctries* 2010; 4(2):070-073.

CASE SHEET PROFORMA

Name:

Age:

Sex:

Address:

IP No. :

Presenting complaints:

H/o Presenting illness:

Fever-duration, continuous/remittent/intermittent,low/moderate/high,treatment

GI symptoms- nausea,vomiting,loss of appetite,pain abdomen,distension,diarrhoea,constipation,bleed etc

Jaundice

Headache

Urine-dysuria,discoloration,frequency

Respiratory symptoms-Cough

Joint pains

CNS symptoms-abnormal movements,altered sensorium,weakness etc

Past History:

Treatment History:

Family History:

Personal History:

Immunization History:

Socioeconomic History:

GENERAL EXAMINATION:

Toxic look-

Pulse-

Blood pressure-

Temperature-

Respiratory Rate-

Pallor-

Icterus-

Lymphadenopathy-

Coated tongue-

SYSTEMIC EXAMINATION

GASTROINTESTINAL SYSTEM

Inspection:Distension,visible veins,pulsations

Palption: Tenderness,Guarding,Rigidity,Liver,Spleen

Percussion: Shifting dullness

Auscultation:Bowel sounds

RESPIRATORY SYSTEM

Inspection:

Palpation:

Percussion:

Auscultation:

CARDIOVASCULAR SYSTEM

Inspection:

Palpation:

Percussion:

Auscultation:

CENTRAL NERVOUS SYSTEM

Higher Mental Functions:

Skull and Spine:

Cranial Nerves:

Motor system:

Sensory system:

Signs of Meningeal irritation:

Cerebellar signs:

Blood Picture: Hemoglobin, Total leucocyte count, Differential count, ESR

Widal test: Positive/ Negative, titer

Blood Culture & sensitivity pattern for Salmonella typhi:

MASTER CHART

							AMPI	CHLORAM	CEFTRI	COTRIMOX	CIPRO	NAL. AC
1	AASHISH .R	I12002806	12 Y	M	+	+	S	S	S	S	S	R
2	GURUDEV	I12003152	10 M	M	+	+	S	S	S	S	S	R
3	KISHOR KUMAR.R	I12005792	4 Y	M	+	-	S	S	S	S	S	R
4	VIGNESH.S	I12009795	3 Y 3 M	M	+	-	S	S	S	S	S	S
5	SAHANAS	I12017315	7 Y	M	+	+	S	S	S	S	S	R
6	SUDARSHAN.S	I12021226	8 Y	M	+	-	S	S	S	S	S	R
7	DHIYA.K	I12023981	10 M	F	+	+	S	S	S	S	S	R
8	VARUN PRASATH.S	I10000710	1 Y 8 M	M	+	-	S	S	S	S	S	R
9	DEEPAK	I10003085	6 Y 3 M	M	+	+	S	S	S	S	S	R
10	GIRIDHARAN.M	I10011264	1O Y	M	+	-	S	S	S	S	S	R

SI	NAME	REG.NO:	AGE	SEX	BLD CUL	WIDAL	ANTIBIOTIC SUSCEPTIBILITY					
							AMPI	CHLORAM	CEFTRI	COTRIMOX	CIPRO	NAL. AC
11	GOKULAKRISHNAN	I10020430	10 Y	M	+	-	S	S	S	S	S	S
12	VANISRI.S.R	I10022478	10 Y 5 M	F	+	-	S	S	S	S	R	R
13	KEERTHANA.L	I10025265	12	F	+	-	S	S	S	S	S	R
14	NANDHA.SM	I10026708	2 Y	M	+	+	S	S	S	S	S	R
15	NITHISH.V	I10027727	5 Y 5 M	M	+	-	S	S	S	S	S	R
16	VEDHANA RAYANAN.K	I10029062	9 Y 10 M	M	+	+	S	S	S	S	S	R
17	SANTHOSH	I10031417	12	M	+	-	S	S	S	S	S	R
18	ARUNACHALAM.E	I10034261	10 Y 3 M	M	+	+	S	S	S	S	S	S
19	MUGUNTHAN.T	I10035848	2 Y	M	+	-	R	S	S	S	S	R
20	SHYRO MARIYA.S	I10047361	2 Y 7 M	F	+	-	S	S	S	S	S	R

SI	NAME	REG.NO:	AGE	SEX	BLD CUL	WIDAL	ANTIBIOTIC SUSCEPTIBILITY					
							AMPI	CHLORAM	CEFTRI	COTRIMOX	CIPRO	NAL. AC
21	MEENA.K	I10048364	4 Y	F	+	+	S	S	S	R	S	R
22	ADITHYA.M	I10051018	9 Y 6M	M	+	-	S	S	S	S	S	R
23	BHARANI PRASANTH	I107010331	13 Y	M	+	+	S	S	S	S	S	R
24	RANJITH	I07015124	12 Y	M	+	+	S	S	S	S	S	R
25	SHEEBA.M	I07016249	8Y 5M	F	+	-	S	R	S	R	R	R
26	SHINY ROMINA	I07017003	8Y 3M	F	+	+	S	S	S	S	S	R
27	LENDA CHRISTINA	I070170271	12 Y	F	+	+	S	S	S	S	S	R
28	JENISHA	I07018371	4Y 8M	F	+	-	S	S	S	S	S	R
29	JOYLYDIA	I07028159	7Y 9M	F	+	-	S	S	S	S	S	R
30	MAHALAKSHMI	I12019525	14Y	F	+	-	S	S	S	S	S	R

SI	NAME	REG.NO:	AGE	SEX	BLD CUL	WIDAL	ANTIBIOTIC SUSCEPTIBILITY					
							AMPI	CHLORAM	CEFTRI	COTRIMOX	CIPRO	NAL. AC
31	THARUN	O07003093	10Y 8M	M	+	-	S	S	S	S	S	R
32	AJMAL	I08002867	5Y	M	+	-	S	S	S	S	S	R
33	SHIVANI.L.M	I08011026	7Y	F	+	-	R	S	S	S	S	R
34	NASEEHA	I08044122	8Y 9M	F	+	+	S	S	S	S	S	R
35	JERVIN THEEYANOSE	I08047632	12Y	M	+	-	S	S	S	S	S	R
36	AJAY CHANDRAN.S	I09020609	5Y 7M	M	+	-	S	S	S	S	S	R
37	DURGA PRASATH.R	I09019187	15 Y	M	+	+	S	S	S	S	S	S
38	MOHAMMED RIYASUDEEN	I09016971	8Y	M	+	-	S	S	S	S	S	R
39	HARISH	I09016948	12Y	M	+	+	S	S	S	S	S	R
40	DINESH.D	I11033985	11Y	M	+	+	S	S	S	S	S	R

SI	NAME	REG.NO:	AGE	SEX	BLD CUL	WIDAL	ANTIBIOTIC SUSCEPTIBILITY					
							AMPI	CHLORAM	CEFTRI	COTRIMOX	CIPRO	NAL. AC
41	ANTONY.D	I11014439	8Y	M	+	-	S	S	S	S	S	R
42	VINDHYA.M	I11017041	11Y	F	+	+	S	S	S	S	S	R
43	EBINEZAR	I11013759	11Y	M	+	-	S	S	S	S	S	R
44	SABARI PRASANNA	I11011217	10 Y	M	+	+	S	S	S	S	S	R
45	DHIVYA.G.B	I11003828	4Y	F	+	-	S	S	S	S	S	R
46	MATHAN.D	I11002198	7Y3M	M	+	+	S	S	S	S	S	R
47	NETHRA.M	O10096185	2Y6M	F	+	-	S	S	S	S	S	R
48	INIYAN.A.S	O07087311	9Y4M	M	+	+	S	S	S	S	S	R
49	YOGESH.M	I11018073	9Y6M	M	+	-	S	S	S	S	R	R
50	SRE SOORYA.K.P	I07037407	14Y	M	+	-	S	S	S	S	S	R

SI	NAME	SYMPTOMS														SIGNS												
		Fe	Ch	Na	Vo	He	Lo	Di	Cn	PA	GIb	Ra	Cg	Jt	Dy	Py	Tx	Ct	Pa	Ja	Ro	Ly	Li	Sp	Js	RS	CN	CV
1	AASHISH .R	+	-	-	-	-	-	+	-	-	-	-	-	-	-	+	-	-	-	-	-	-	+	+	-	-	-	-
2	GURUDEV	+	-	-	+	-	-	-	-	+	-	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-	-
3	KISHOR KUMAR.R	+	-	+	-	+	-	-	-	-	-	-	+	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-
4	VIGNESH.S	+	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	+	+	-	-	-	-
5	SAHANAS	+	+	-	-	-	-	+	-	-	-	-	-	-	-	+	-	-	+	-	-	-	+	-	-	-	-	-
6	SUDARSHAN.S	+	-	-	+	-	-	+	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
7	DHIYA.K	+	-	-	-	-	-	-	-	-	-	-	+	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-
8	VARUN PRASATH.S	+	-	-	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	+	-	-	-	-
9	DEEPAK	+	-	-	+	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-
10	GIRIDHARAN.M	+	-	-	+	-	-	-	-	-	-	-	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-

SI	NAME	SYMPTOMS														SIGNS												
		Fe	Ch	Na	Vo	He	Lo	Di	Cn	PA	GIb	Ra	Cg	Jt	Dy	Py	Tx	Ct	Pa	Ja	Ro	Ly	Li	Sp	Js	RS	CN	CV
11	GOKULAKRISHNAN	+	-	-	+	-	-	+	-	-	-	-	-	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-
12	VANISRI.S.R	+	-	-	-	-	-	-	-	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
13	KEERTHANA.L	+	-	-	-	-	-	-	-	-	-	-	+	-	-	+	+	-	-	-	-	-	+	+	-	-	-	-
14	NANDHA.SM	+	+	-	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-
15	NITHISH.V	+	-	-	+	-	+	+	-	+	-	-	-	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-
16	VEDHANARAYANAN.K	+	-	-	+	-	-	-	-	-	-	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-	-
17	SANTHOSH	+	-	-	+	-	-	+	-	-	-	-	+	-	-	+	-	-	-	-	-	-	+	+	-	-	-	-
18	ARUNACHALAM.E	+	-	-	-	-	-	-	-	+	-	-	-	-	-	+	-	-	-	+	-	-	-	+	-	-	-	-
19	MUGUNTHAN.T	+	+	-	+	+	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-	-	+	-	-	-	-	-
20	SHYRO MARIYA.S	+	-	-	+	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-

SI	NAME	SYMPTOMS														SIGNS												
		Fe	Ch	Na	Vo	He	Lo	Di	Cn	PA	GIb	Ra	Cg	Jt	Dy	Py	Tx	Ct	Pa	Ja	Ro	Ly	Li	Sp	Js	RS	CN	CV
21	MEENA.K	+	-	-	-		-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
22	ADITHYA.M	+	-	-	+	-	-	-	-	-	-	-	-	-	-	+	-	+	+	-	-	-	+	+	-	-	-	-
23	BHARANI PRASANTH	+	-	-	-	-	-	-	-	-	-	-	+	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-
24	RANJITH	+	-	-	+	-	-	+	-	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
25	SHEEBA.M	+	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
26	SHINY ROMINA	+	-	-	+	-	-	+	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	+	-	-	-	-
27	LENDA CHRISTINA	+	-	-	-	-	-	-	-	+	-	-	-	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-
28	JENISHA	+	-	-	-	-	-	+	-	-	-	-	-	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-
29	JOYLYDIA	+	+	-	+	-	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-
30	THARUNESWAR.J	+	-	-	-	-	-	-	-	-	-	-	+	-	-	+	-	-	-	-	-	-	+	+	-	-	-	-

SI	NAME	SYMPTOMS														SIGNS												
		Fe	Ch	Na	Vo	He	Lo	Di	Cn	PA	GIb	Ra	Cg	Jt	Dy	Py	Tx	Ct	Pa	Ja	Ro	Ly	Li	Sp	Js	RS	CN	CV
31	THARUN	+	-	-	+	-	-	-	-	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
32	AJMAL	+	+	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-
33	SHIVANI.L.M	+	-	-	+	-	-	+	-	-	-	-	+	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-
34	NASEEHA	+	-	-	-	-	-	-	-	+	-	-	-	-	+	+	-	-	-	-	-	-	+	+	-	-	-	-
35	JERVIN THEEYANOSE	+	-	-	+	-	+	-	-	-	-	-	+	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-
36	AJAY CHANDRAN.S	+	-	-	+	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-
37	DURGA PRASATH.R	+	-	-	-	-	-	-	-	-	-	-	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
38	MOHAMMED RIYASUDEEN	+	-	-	+	-	-	-	-	+	-	-	-	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-
39	HARISH	+	-	-	-	-	-	+	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	+	-	-	-	-
40	DINESH.D	+	-	-	+	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-

SI	NAME	SYMPTOMS														SIGNS												
		Fe	Ch	Na	Vo	He	Lo	Di	Cn	PA	GIb	Ra	Cg	Jt	Dy	Py	Tx	Ct	Pa	Ja	Ro	Ly	Li	Sp	Js	RS	CN	CV
41	ANTONY.D	+	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
42	VINDHYA.M	+	-	-	+	-	-	+	-	+	-	-	-	-	-	+	+	-	-	-	-	-	-	+	-	-	-	-
43	EBINEZAR	+	-	-	-	-	-	-	-	-	-	-	+	-	-	+	-	-	-	-	-	-	+	+	-	-	-	-
44	SABARI PRASANNA	+	-	-	-	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-
45	DHIVYA.G.B	+	-	-	+	-	-	-	-	-	-	-	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
46	MATHAN.D	+	-	-	-	-	+	-	-	+	-	-	-	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-
47	NETHRA.M	+	-	-	-	-	-	-	-	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	+	-	-	-
48	INIYAN.A.S	+	-	+	+	-	-	-	-	-	-	-	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
49	YOGESH.M	+	-	-	-	-	-	-	-	-	-	-	+	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-
50	SRE SOORYA.K.P	+	+	-	-	+-	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-

MASTER CHARTS KEY WORDS

BLD CUL	-	BLOOD CULTURE
AMPI	-	AMPICILLIN
CHLORAM	-	CHLORAMPHENICOL
CEFTRI	-	CEFTRIAXONE
COTRIMOX	-	COTRIMOXAZOLE
CIPRO	-	CIPROFLOXACIN
NAL.AC	-	NALIDIXIC ACID
Fe	-	FEVER
Ch	-	CHILLS
Na	-	NAUSEA
Vo	-	VOMITING
He	-	HEADACHE
Lo	-	LOSS OF APPETITE
D	-	DIARRHEA
Cn	-	CONSTIPATION
PA	-	PAIN ABDOMEN
GIb	-	G.I.BLEED
Ra	-	RASH
Cg	-	COUGH
Jt	-	JOINT PAIN
Dy	-	DYSURIA
Py	-	PYREXIA

Tx	-	TOXIC LOOK
Ct	-	COATED TONGUE
Pa	-	PALLOR
Ja	-	JAUNDICE
Ro	-	ROSE SPOTS
Ly	-	LYMPHADENOPATHY
Hep	-	HEPATOMEGALY
Sp	-	SPLENOMEGALY
Js	-	JOINT SWELLING
CV	-	CARDIOVASCULAR SYSTEM
RS	-	RESPIRATORY SYSTEM
CN	-	CENTRAL NERVOUS SYSTEM
GIb	-	G.I.BLEED